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Ambient Water Quality Criteria for Polychlorinated Biphenyls

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16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Polychlorinated Biphenyls (PCBs). It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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AMBIENT WATER QUALITY CRITERIA FOR
POLYCHLORINATED BIPHENYLS

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Water Regulations and Standards
Criteria and Standards Division
Washington, D.C.

Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
Washington, D.C.

Environmental Research Laboratories
Corvalis, Oregon
Duluth, Minnesota
Gulf Breeze, Florida
Narragansett, Rhode Island

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
Deputy Assistant Administrator
Office of Water Regulations and Standards

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Aquatic Life Toxicology

Charles E. Stephan, ERL-Duluth
U.S. Environmental Protection Agency

David J. Hansen, ERL-Duluth
U.S. Environmental Protection Agency

Mammalian Toxicity and Human Health Effects

Jonathan Ward (author)
University of Texas

Steven D. Lutkenhoff (doc. mgr.), ECAO
U.S. Environmental Protection Agency

Bonnie Smith (doc. mgr.), ECAO-Cin
U.S. Environmental Protection Agency

Patrick Durkin
Syracuse Research Corporation

Alfred Garvin
University of Cincinnati

Betty Herndon
Midwest Research Institute

Steven D. Lutkenhoff, ECAO-Cin
U.S. Environmental Protection Agency

Anne Trontell
Energy Resources Co., Inc.

Robert Willes
Health and Welfare
Canada

Karen Blackburn, HERL
U.S. Environmental Protection Agency

Norman Clarke, HERL
U.S. Environmental Protection Agency

Diane Courtney- ECAO-RTP
U.S. Environmental Protection Agency

Larry Fradkin, ECAO-Cin
U.S. Environmental Protection Agency

Rolf Hartung
University of Michigan

Larry Lowry
National Institute of Occupational
Safety and Health

Albert E. Munson
Medical College of Virginia

Walter Weigel
National Institute of Occupational
Safety and Health

Roy E. Albert*
Carcinogen Assessment Group
U.S. Environmental Protection Agency

Technical Support Services Staff: D.J. Reisman, M.A. Garlough, B.L. Zwayer, P.A. Daunt, K.S. Edwards, T.A. Scandura, A.T. Pressley, C.A. Cooper, M.M. Denessen.

Clerical Staff: C.A. Haynes, S.J. Faehr, L.A. Wade, D. Jones, B.J. Bordicks, B.J. Quesnell.

*CAG Participating Members:
Elizabeth L. Anderson, Larry Anderson, Dolph Arnicar, Steven Bayard, David L. Bayliss, Chao W. Chen, John R. Fowle III, Bernard Haberman, Charalingayya Hiremath, Chang S. Lao, Robert McGaughy, Jeffrey Rosenblatt, Dharm V. Singh, and Todd W. Thorslund.

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CRITERIA DOCUMENT

POLYCHLORINATED BIPHENYLS

CRITERIA

Aquatic Life

For polychlorinated biphenyls the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.014 µg/l as a 24-hour average. The concentration of 0.014 µg/l is probably too high because it is based on bioconcentration factors measured in laboratory studies, but field studies apparently produce factors at least ten times higher for fishes. The available data indicate that acute toxicity to freshwater aquatic life probably will only occur at concentrations above 2.0 µg/l and that the 24-hour average should provide adequate protection against acute toxicity.

For polychlorinated biphenyls the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.030 µg/l as a 24-hour average. The concentration of 0.030 µg/l is probably too high because it is based on bioconcentration factors measured in laboratory studies, but field studies apparently produce factors at least ten times higher for fishes. The available data indicate that acute toxicity to saltwater aquatic life probably will only occur at concentrations above 10 µg/l and that the 24-hour average criterion should provide adequate protection against acute toxicity.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of polychlorinated biphenyls through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentration should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 0.79 ng/l, 0.079 ng/l, and 0.0079 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, exluding consumption of water, the levels are 0.79 ng/l, 0.079 ng/l, and 0.0079 ng/l, respectively.

INTRODUCTION

Polychlorinated biphenyls (PCBs) are the chlorinated derivatives of a class of aromatic organic compounds called biphenyls and are manufactured by the direct chlorination of the biphenyl ring system. The commercial products are complex mixtures of chlorobiphenyls and are marketed for various uses according to the percentage of chlorine in the mixture. Currently there is no production of PCBs in the United States but the sole producer of PCBs in the United States previously marketed four mixtures containing 21 percent, 41 percent, 42 percent, and 54 percent chlorine for use only in closed electrical systems under the registered trademark Aroclor. Prior to 1971, mixtures containing up to 68 percent chlorine were used in a number of other applications, including plasticizers, heat transfer fluids, hydraulic fluids, fluids in vacuum pumps and compressors, lubricants, and wax extenders.

In 1974 approximately 65 to 70 percent of domestic sales were to manufacturers of capacitors and the remainder to manufacturers of transformers while approximately 450,000 pounds of PCBs were imported primarily for use in non-closed systems. Production in the United States appeared to be one-half of the world total.

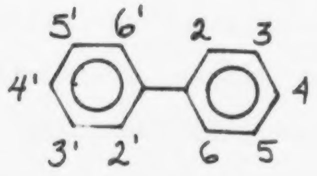
As a result of the long life of many products containing PCBs, it is believed that a substantial portion of the PCBs manufactured before 1971 are still in service and thus represent potential pollution through possible future discharge into the environment.

During the period 1972 to 1974, domestic production of PCBs averaged approximately 40 million pounds per year with 33 million pounds representing the annual domestic marketed consumption during that period.

Although the environmental behavior and biological activity of a number of individual chlorobiphenyl isomers have been studied in recent years, it is still difficult to evaluate the potential toxicity of the complex mixtures actually found in the environment since their composition often changes. In making this evaluation it is necessary to weigh carefully the results of studies of individual compounds, and to compare critically the environmental and toxicological properties of the commercial mixtures.

A further complication is that several commercial PCB mixtures have been reported to contain small quantities of highly toxic contaminants, polychlorinated dibenzofurans (PCDFs). Certain of the toxic effects observed in animals and humans exposed to PCBs appear to be attributable to PCDFs, while others appear to be caused by PCBs themselves. There is also some evidence that small quantities of PCDFs may be formed from PCBs while in service or as a result of metabolic changes in certain organisms.

PCBs consist of a mixture of chlorinated biphenyls which contain a varying number of substituted chlorine atoms on the aromatic rings. The biphenyl molecule has a total of ten sites where chlorine substitution can be accommodated as shown in the following structure:



The potential positions for chlorine substitution are numbered according to the American Chemical Society standard notation. Chlorinated biphenyls having the same number of chlorine atoms per molecule are referred to as a specific class of chlorobiphenyls, with a suitable numerical prefix to define the number of substituted chlorines. Hence, there are classes varying from monochlorobiphenyls to decachlorobiphenyls. All compounds within the same class have the same molecular weight and are structural isomers of each other. They differ only in terms of the location of the chlorine atoms in the biphenyl ring. The ten classes of chlorobiphenyls, comprising 209 possible isomers, are summarized in Table 1.

Chlorobiphenyls with five or more chlorine atoms are referred to as "higher chlorobiphenyls." This distinction is made in recognition of the fact that the former group of compounds is much more persistent in the environment than the latter group. The tetrachlorobiphenyls are intermediate in persistence.

The physical properties of individual chlorinated biphenyls are known (Cook, 1972). The physical properties of the Aroclor mixtures are summarized in Table 2. Lower chlorinated Aroclors (1221, 1232, 1016, 1242, and 1248) are colorless mobile oils. Increasing chlorine content results in mixtures taking on the consistency of viscous liquids (Aroclor 1254) or sticky resins (Aroclors 1260 and 1262). Aroclors 1268 and 1270 are of white powders. With the exception of Aroclors 1221 and 1268, Aroclors do not crystallize upon heating or cooling but at a specific temperature, defined as a "pour point," change into a resinous state.

TABLE 1

Empirical Formulation, Molecular Weights, and Chlorine Percentage in PCBs[a]

Empirical Formula Chlorobiphenyls	Molecular Weight[b]	Percent Chlorine[b]	No. of Isomers
$C_{12}H_{10}$	154	0	1
$C_{12}H_9Cl$	188	18.6	3
$C_{12}H_8Cl_2$	222	31.5	12
$C_{12}H_7Cl_3$	256	41.0	24
$C_{12}H_6Cl_4$	290	48.3	42
$C_{12}H_5Cl_5$	324	54.0	46
$C_{12}H_4Cl_6$	358	58.7	42
$C_{12}H_3Cl_7$	392	62.5	24
$C_{12}H_2Cl_8$	426	65.7	12
$C_{12}H_1Cl_9$	460	68.5	3
$C_{12}Cl_{10}$	490	79.9	1

[a] Source: Hutzinger, et al. 1974

[b] Based on Cl

TABLE 2

Physical Properties of Commercial PCBs (Aroclors)*

Property	1221	1232	1016	1242	1248
Chlorine, percent	20.5-21.5	31.4-32.5	41	42	48
Specific Gravity	1.182-1.192 ($25^{o}/15.5^{o}C$)	1.270-1.280 ($25^{o}/15.5^{o}C$)	1.362-1.372 ($25^{o}/15.5^{o}C$)	1.391-1.392 ($25^{o}/15.5^{o}C$)	1.405-1.415 ($65^{o}/15.5^{o}C$)
Distillation Range ^{o}C Corrected	275-320	290-325	323-356	325-366	340-375
Vapor Pressure (mm/HS)				$4.06x10^{-4}$	$4.94x10^{-4}$
Evaporation loss (%) $100^{o}C$ 6 hr.	1.0-1.5	1.0-1.5		0-0.4	0-0.3
USTA D-6 Mod. $160^{o}C$, 5 hr.				3.0-3.6	3.0-4.0
Pour Point^{o}C (WTM E97) F	1 (Crystal) 34 (Crystal)	-35.5 -32		-19 2	-7 19.4
Water Solubility at $25^{o}C$(μg/l)	200		225-250	240	54

TABLE 2 (cont.)

Physical Properties of Commercial PCBs (Aroclors)*

Property	1254	1260	1262	1268	1270
Chlorine, percent	54	60	61.5-62.5	68	71
Specific Gravity	1.495-1.555 (65°/15.5°C)	1.555-1.566 (90°/15.5°C)	1.572-1.583 (90°/15.5°C)	1.604-1.611 (25°/25°C)	1.944-1.960 (25°/25°C)
Distillation Range °C Corrected	365-390	385-420	390-425	435-450	450-460
Vapor Pressure (mm/HS)	7.71×10^{-5}	4.05×10^{-5}			
Evaporation loss (%) 100°C 6 hr.	0-0.2	0-0.1	0-0.1	0-0.6	
USTA D-6 Mod. 160°C, 5 hr.	1.1-1.3	0.5-0.8	0.5-0.2	0.1-0.2	
Pour Point °C (WTM E97) F	10 50	31 88	35-38 99		
Water Solubility at 25°C(μg/l)	12	2.7			

*Source: Versar, Inc., 1976
Hutzinger, et al. 1974
Mieure, et al. 1976
Tucker, et al. 1975
Mackay and Wolkoff, 1973

It is known from the studies of pesticides that soil moisture and evaporation of water have a strong influence on the rate of chlorinated hydrocarbon volatilization from soils and sand. Haque, et al. (1974) demonstrated that the periodic evaporation of water from Ottawa sand enhanced the total volatilization of Aroclor 1254 but reduced the degree of differentiation in the volatility of the higher chlorinated biphenyls (7, 6, and 5 chlorine aroms) from the tetrachlorobiphenyls. However, when Aroclor 1254 was heated in water at 100°C the total volatilization of this Aroclor was reduced compared to equivalent dry isothermal conditions, but the differentiation in volatility between the higher and lower chlorinated biphenyls was increased (Bowes, et al. 1975).

Mackay and Wolkoff (1973) calculated theoretical evaporation rates for various Aroclors from water and predicted very rapid volatilization rates. Under laboratory conditions, PCBs appear to volatilize fairly rapidly from water in aquaria (Uhlken, et al. 1973) and even from flasks plugged with glass wool (Oloffs, et al. 1972). Under the same conditions, volatilization was markedly reduced in the presence of sediments (Oloffs, et al. 1973). Hence in natural waters, it would seem likely that absorption to sediments would limit the rate of volatilization.

Solubilities of the individual chlorinated biphenyls in water have been studied by several workers and an inverse correlation between solubility and degree of chlorination has been reported (Wollnofer, et al. 1973; Haque and Schmedding, 1975; Metcalf, et al. 1975). The problem in obtaining true solution equilibria data for PCBs in water has been explained by Schoor (1975) who has given evidence that solutions of PCBs in water are in fact stable emulsions of PCB aggregates and that the true solubility of Aroclor 1254 is less than 0.1 μg/l in fresh water and 0.04 μg/l in marine water.

Chlorobiphenyls are freely soluble in relatively nonpolar organic solvents (Hutzinger, et al. 1974) and lipids in biological systems (Metcalf, et al. 1975). Metcalf, et al. have reported octanol/water partition coefficients in the range of 10,000 to 20,000 for representative tri-, tetra-, and pentachlorobiphenyls. Partition coefficients with this biphasic solvent system have been found to correlate well with ecological magnification factors in aquatic organisms (Metcalf, et al. 1975).

PCBs are strongly adsorbed on solid surfaces, including glass and metal surfaces in laboratory apparatus (Schoor, 1975) and soils, sediments, and particulates in the environment (Haque, et al. 1974; Oloffs, et al. 1973; Crump-Wiesner, et al. 1974; Dennis, 1976; Munson, et al. 1976; Pfister, et al. 1969).

In aquatic environments, PCBs are associated with sediments and are usually found at much higher concentrations in sediments than in water in contact with them (Young, et al. 1976; Crump-Weisner, et al. 1974; Dennis, 1976). As with other chlorinated hydrocarbons, PCBs are probably associated particularly strongly with micro-particulates of 0.15 μm diameter or less (Pfister, et al. 1969).

PCBs are commercially produced by the chlorination of the biphenyl ring with anhydrous chlorine in the presence of iron filings or ferric chloride as the catalyst. The crude product is purified to remove the color and traces of the by-product hydrogen chloride, and the catalyst by treatment with alkali and subsequent distillation. The purified product is a complex mixture of the chlorobiphenyls, the precise composition depending on the conditions under which the chlorination occurred.

It has been reported that foreign PCB mixtures are similar in composition to one of the 10 Aroclor products previously manufactured in the U.S. Gas liquid chromatograms of Phenoclor DP6 (France), Clopen A60 (Germany), and Aroclor 1260 (U.S.), all mixtures containing 60 percent chlorine, show that these mixtures are virtually identical (Tas and de Vos, 1971). Jensen and Sundstron (1974) have shown that Clophen A60 and A50 (Germany) are very similar in isomer composition to Aroclors 1260 and 1254 (U.S.), respectively. Table 3 lists the distribution of the various classes of chlorobiphenyls in seven major Aroclor mixtures as reported by Mieure, et al. (1976), Webb and McCall (1973), and Hirwe, et al. (1974). The small differences in analytical results reported for Aroclors 1242 and 1254 may reflect either differences in analytical methods or variations in sample constitution.

Certain substitution patterns are believed to influence the biological activities of chlorobiphenyls. The presence of two adjacent carbon atoms without chlorine substitution in one or both rings is believed to facilitate metabolism because it permits the formation of arene oxide intermediates (Safe, et al. 1975). Essentially all chlorobiphenyls with five or fewer chlorine atoms have at least one pair of adjacent unsubstituted carbon atoms because of the rarity of 3,5-substitution in the natural mixtures.

TABLE 3

Approximate Molecular Composition of Aroclors (%)

Chlorobiphenyl	1221		1232	1016	1242			1248		1254		1260
	1	2	2	1	1	2	3	2	1	2	3	2
$C_{12}H_{10}$	11	7	6	Tr	Tr	-	-	-	Tr	-	-	-
$C_{12}H_9Cl$	51	51	26	1	1	1	Tr	-	Tr	-	-	-
$C_{12}H_8Cl_2$	32	38	29	20	16	17	4	1	0.5	-	-	-
$C_{12}H_7Cl_3$	4	3	24	57	49	40	39	23	1	-	0.5	-
$C_{12}H_6Cl_4$	2	-	15	21	25	32	42	50	21	16	36	-
$C_{12}H_5Cl_5$	0.5	-	0.5	1	8	10	14	20	48	60	45	12
$C_{12}H_4Cl_6$	-	-	-	Tr	1	0.5	-	1	23	23	18	46
$C_{12}H_3Cl_7$	-	-	-	-	Tr	-	-	-	6	1	1	36
$C_{12}H_2Cl_8$	-	-	-	-	-	-	-	-	-	-	-	6
$C_{12}H_1Cl_9$	-	-	-	-	-	-	-	-	-	-	-	-
$C_{12}Cl_{10}$	-	-	-	-	-	-	-	-	-	-	-	-

Tr - Trace (< 0.1 percent)

Source: [1]Mieure, et al. 1976

[2]Webb and McCall, 1973

[3]Hirwe, et al. 1974

Jensen and Sundstrom (1974) presented evidence that chlorobiphenyls with three or four chlorine atoms in the ortho- positions (2- and 6- positions) are more easily metabolized by humans than those with only one or two ortho-chlorines. Compounds with three or four ortho- substituted chlorines are virtually absent from Aroclors 1016 and 1242 but are fairly well represented in Aroclors 1254 and 1260 (Clopens A50 and A60, respectively).

McKinney (1976) has suggested that chlorobiphenyl isomers with chlorine substitution in both the 4- and 4' positions tend to be biologically active and well retained in tissues. The number and proportion of these isomers increase with increasing chlorination.

McKinney, et al. (1976) have shown an association between biological activity and substitutions in the 3,4- or 3,4,5- positions on one or both rings. The first pattern is frequently found in PCB mixtures but the second is found only as part of the 2,3,4,5-pattern which is found in only trace amounts in PCBs.

Toxic materials other than chlorinated biphenyls have been found in commercial PCB mixtures. Vos, et al. (1970), Bowes, et al. (1975), Roach and Pomerantz (1974), Nagayama, et al. (1976), and Kuratsune, et al. (1976) have detected polychlorinated dibenzofurans (PCDFs) in a number of domestic and foreign PCB mixtures at levels of 0.8 to 33 mg/kg. While 119 structurally different PCDF isomers are possible, only two have been precisely identified to date, the 2,3,7,8-tetrachloro- and the 2,3,4,7,8-pentachlorodibenzofurans (Bowes, et al. 1975).

Polychlorinated naphthalenes (PCNs) have also been identified in small quantities in Clopen A60 and Phenochlor DP 6 (both corresponding to Aroclor 1260), Aroclor 1254, and KC-400 (corresponding to Aroclor 1248) (Vos, et al. 1970; Roach and Pomerantz, 1974; Bowes, et al. 1975).

There appear to be no authenticated reports of polychlorinated dibenzo-p-dioxins (PCDDs) in commercial PCBs (Bowes, et al. 1975). The presence of potentially toxic compounds other than polychlorinated biphenyls in commercial PCB mixtures complicates both analytical and toxicological evaluation of such mixtures.

PCBs are considered to be inert to almost all of the typical chemical reactions. PCBs do not undergo oxidation, reduction, addition, elimination, or electrophilic substitution reactions except under extreme conditions. Chlorines can be replaced by reductive dechlorination with any metal hydride such as lithium aluminum hydride but temperatures of 245°C or greater are required to effect chlorine displacement.

The reactions of environmental importance that PCBs appear to undergo include alkali- and photochemically-catalyzed nucleophilic substitutions and photochemical free radical substitutions, all of which occur with alkali and water.

Photolysis generally has been found to give one type of product under environmental conditions (Hutzinger, et al. 1972, 1974; Ruzo, et al. 1972, 1974; Ruzo and Zabik, 1975; Herring, et al. 1972). Chlorine is replaced by hydroxy groups in aqueous systems.

A marked increase in rate of PCB photolysis was observed when solvents were degassed prior to irradiation (Ruzo, et al. 1974).

Oxygen is known to act as a free radical quencher by accepting energy from free radicals before any chemical change can occur. This increase in rate therefore implies that a free radical process is occurring and in the environment these photochemical transformations will be enhanced under anaerobic conditions.

The photochemical behavior of higher chlorobiphenyls appears similar to that of the tetrachlorobiphenyls (Hutzinger, et al. 1972; Herring, et al. 1972). Irradiation of Aroclor 1254 in aqueous solution gave rise to dechlorinated and hydroxylated products (Hutzinger, et al. 1972). Hexa- and octachlorobiphenyls are more photochemically reactive than tetrachlorobiphenyls, so that under irradiation the higher components of Aroclor 1254 are selectively degraded (Hutzinger, et al. 1972; Herring, et al. 1972).

The creation of free radicals by sunlight allows the environmental replacement of chlorines by hydroxy groups from water without the intervention of alkali. When this occurs at the ortho-position (found to be the most preferred for chlorine loss) the resulting 2-hydroxychlorobiphenyl is perfectly positioned to allow oxygen to bond to an ortho- position of the other ring. This results in the creation of potentially the most important class of contaminant in commercial mixtures of PCBs, the chlorodibenzofurans (CDFs).

Irradiation studies on either Aroclor 1254 or 2,5,2',5'-tetrachlorobiphenyl (Hutzinger, et al. 1972) in hydroxylic solvents have shown the formation of phenolic compounds, carboxylic compounds, and polymers along with dechlorination. Activation of the phenyl rings by metals or metallic salts make them more susceptible to hydroxylation. Thus, in the environment, either heat, light, or metals and metal salts in water could theoretically accelerate the transformation of PCBs to PCDFs. The ultraviolet component of sunlight is sufficiently energetic to generate free radicals from both phenols and PCBs. The energies required to break the Ar-Cl bond to form hydroxy-PCBs in a hydroxylic solvent and ArO-H bond to form CDFs correspond to wavelengths near 360 to 320 nm, respectively. These wave lengths are clearly within the sunlight region.

Irradiation experiments with five pure 2-chlorinated biphenyls as 5 mg/l aqueous suspensions, showed that traces of 2-chlorodibenzofuran were detectable although only the 2,5-dichloro- and the 2,5,2',5'-tetrachlorobiphenyls provided identifiable amounts or approximately a 0.2 percent yield during a seven-day irradiation (Crosby, et al. 1973; Crosby and Moilanen, 1973). The environmental significance of this is fourfold: (1) ortho-chlorobiphenyls can be hydroxylated by radiation similar to sunlight when they are suspended in aqueous media; (2) the product(s) are converted to CDFs; (3) rates of CDF formation by this process are approximately the same as their rates of degradation, leading to an approximately steady concentration; and (4) decomposition of 2,8-dichlorobenzofuran was found to be very slow in aqueous suspension but dehalogenation did not take place to form the relatively photolytically stable 2-chlorodibenzofuran (Crosby and Moilanen, 1973).

In addition to photochemical and metallic salt formations of PCDFs from PCBs, a third route of formation has been suggested. Kanechlor KC-400 (analogous to Aroclor 1248) having an intitial

PCDF content of 20 mg/kg, was shown to undergo conversion as the heat transfer fluid in a heat exchanger to give PCBs with a PCDF content of 4,975 to 11,765 mg/kg (Nagayma, et al. 1976; Kuratsune, et al. 1976). This material was identified as the agent which poisoned a large number of Japanese in 1968. A general disadvantage of PCBs in many of their applications including electrical capacitor and transformer uses as well as heat transfer uses is their tendency to decompose under the action of heat or electrical arcing to form potentially more toxic products (Broadhurst, 1972).

REFERENCES

Bowes, G.W., et al. 1975. Identification of chlorinated dibenzofurans in American polychorinated biphenyls. Nature. 256: 305.

Broadhurst, M.G. 1972. Use and replaceability of polychlorinated biphenyls. Environ. Health Perspect. 2: 81.

Cook, J.W. 1972. Some chemical aspects of polychlorinated biphenyls (PCBs). Environ. Health Perspect. 1: 1.

Crosby, D.G., et al. 1973. Environmental generation and degradation of dibenzodioxins and dibenzofurans. Environ. Health Perspect. 5: 259.

Crosby, D.H. and K.W. Moilanen. 1973. Photodecomposition of chlorinated biphenyls and dibenzofurans. Bull. Environ. Contam. Toxicol. 10: 372.

Crump-Wiesner, H.J., et al. 1974. Pesticides in water: A study of the distribution of polychlorinated biphenyls in the aquatic environment. Pestic. Monitor. Jour. 8: 157.

Dennis, D.S. 1976. Polychlorinated biphenyls in the surface waters and bottom sediments of the major basins of the United States. Proc. Natl. Conf. on Polychlorinated Biphenyls. p. 193.

Haque, R. and D. Schmedding. 1975. A method of measuring the water solubility of hydrophobic chemicals: Solubility of five polychlorinated biphenyls. Bull. Environ. Contam. Toxicol. 14: 13.

Haque, R., et al. 1974. Aqueous solubility, adsorption, and vapor behavior of polychlorinated biphenyl Aroclor 1254. Environ. Sci. Technol. 8: 139.

Herring, J.L., et al. 1972. UV irradiation of Aroclor 1254. Bull. Environ. Contam. Toxicol. 8: 153.

Hirwe, S.N., et al. 1974. Gas-liquid chromatography-mass spectrometric characterization of Aroclor 1242 and 1254 components. Bull. Environ. Contam. Toxicol. 12: 135.

Hutzinger, O., et al. 1972. Photochemical degradation of chlorobiphenyls (PCBs). Environ. Health Perspect. 1: 15.

Hutzinger, O., et al. 1974. The Chemistry of PCBs. CRC Press, Cleveland, Ohio.

Jensen, S. and G. Sundstrom. 1974. Structures and levels of most chlorobiphenyls in two technical PCB products and in human adipose tissue. Ambio. 3: 70.

Kuratsune, M., et al. 1976. Some of the recent findings concerning Yusho. Proc. Natl. Conf. on Polychlorinated Biphenyls. p. 15.

Mackay, D. and A.W. Wolkoff. 1973. Rate of evaporation on low-solubility contaminants from water bodies to atmosphere. Environ. Sci. Technol. 7: 611.

McKinney, J.D. 1976. Toxicology of selected symmetrical hexachlorobiphenyl isomers: Correlating biological effects with chemical structure. Proc. Natl. Conf. on Polychlorinated Biphenyls. p. 99.

McKinney, J.D., et al. 1976. Toxicology of hexachlorobiphenyl isomers and 2,3,7,8-tetrachlorodibenzofuran in chicks. I. Relationship of chemical parameters. Toxicol. Appl. Pharmacol. (In press)

Metcalf, R.L., et al. 1975. Laboratory model ecosystem studies of the degradation and fate of radiolabeled tri-, tetra-, and pentachlorobiphenyl compared with DDE. Arch. Environ. Contam. Toxicol. 3: 151.

Mieure, J.P., et al. 1976. Characterization of polychlorinated biphenyls. Proc. Natl. Conf. on Polychlorinated Biphenyls. p. 112.

Munson, T.O., et al. 1976. Transport of chlorinated hydrocarbons in the Upper Chesapeake Bay. Proc. Natl. Conf. on Polychlorinated Biphenyls. p. 223.

Nagayama, J., et al. 1976. Determination of chlorinated dibenzofurans in Kanechlors and "Yusho Oil". Bull. Environ. Contam. Toxicol. 15: 9.

Oloffs, P.C., et al. 1972. Fate and behavior of five chlorinated hydrocarbons in three natural waters. Can. Jour. Microbiol. 18: 1393.

Oloffs, P.C., et al. 1973. Factors affecting the behavior of five chlorinated hydrocarbons in the two natural waters and their sediments. Jour. Fish. Res. Board Can. 30: 1619.

Pfister, R.M., et al. 1969. Microparticulates: Isolation from water and identification of associated chlorinated pesticides. Science. 166: 878.

Roach, J.A.G. and I.H. Pomerantz. 1974. The finding of chlorinated dibenzofurans in a Japanese polychlorinated biphenyl sample. Bull. Environ. Contam. Toxicol. 12: 338.

Ruzo, L.O. and M.J. Zabik. 1975. Polyhalogenated biphenyls: Photolysis of hexabromo and hexachlorobiphenyls in methanol solution. Bull. Environ. Contam. Toxicol. 13: 181.

Ruzo, L.O., et al. 1972. Polychlorinated biphenyls: Photolysis of 3,4,3',4'-tetrachlorobiphenyl and 4,4'-dichlorobiphenyl in solution. Bull. Environ. Contam. Toxicol. 8: 217.

Ruzo, L.O., et al. 1974. Photochemistry of bioactive compounds: Photo-products and kinetics of polychlorinated biphenyls. Jour. Agric. Food Chem. 22: 199.

Safe, S., et al. 1975. The mechanism of chlorobiphenyl metabolism. Jour. Agric. Food Chem. 28: 851.

Schoor, W.P. 1975. Problems associated with low-solubility compounds in aquatic toxicity tests: theoretical model and solubility characteristics of Aroclor 1254 in water. Water Res. 9: 937.

Tas, A.C. and R.H. deVos. 1971. Characterization of four major components in a technical polychlorinated biphenyl mixture. Environ. Sci. Technol. 5: 1216.

Tucker, E.S., et al. 1975. Migration of polychlorinated biphenyls in soil induced by percolating water. Bull. Environ. Contam. Toxicol. 13: 86.

Uhlken, L.D., et al. 1973. Apparent volatility of PCBs as used in continuous flow bioassays. PCB Newsletter. 5: 4.

Versar, Inc. 1976. Final Report. PCBs in the United States: Industrial use and environmental distribution. Report to U.S. Environmental Protection Agency. Task I. Contract No. 68-01-3259.

Vos, J.G., et al. 1970. Identification and toxicological evaluation of chlorinated benzofuran and chlorinated naphthalene in two commercial polychlorinated biphenyls. Food Cosmet. Toxicol. 8: 625.

Webb, R.G. and A.C. McCall. 1973. Quantitative PCB standards for electron capture gas chromatography. Jour. Chromatog. Sci. 11: 366.

Wollnofer, P.R., et al. 1973. The solubilities of twenty-one chlorobiphenyls in water. Analabs Research Notes. 13: 14.

Young, D.R., et al. 1976. Marine inputs of polychlorinated biphenyls off southern California. Proc. Natl. Conf. on Polychlorinated Biphenyls. p. 197.

Aquatic Life Toxicology*

INTRODUCTION

Most data for polychlorinated biphenyls (PCBs) found in the literature are from studies concerned with tissue levels in fish, mammals, and birds, without correlation with source or exposure concentrations. Many studies dealing with various physiological parameters are also available but, again, are such that they are of little use here. Also, PCBs often do not appear to be very acutely toxic to juvenile and adult freshwater fish and invertebrate species in static tests due to low solubility, and this can lead to erroneous judgments as to the actual toxicity of the compounds.

PCBs occur as mixtures of chemical isomers that differ in the amount of chlorination of the biphenyl structure; they have been treated herein as a single entity. Polychlorinated biphenyls were manufactured by the direct chlorination of biphenyl; production in the United States has now ceased. These mixtures were identified under the trade names Aroclor® and capacitor®, and sold on the basis of percentage chlorine (e.g., 21, 42, 54, and 60 percent). Because each component of the mixtures differs slightly in its physical, chemical, and biological properties, and because a possible 209 different chlorobiphenyls may be produced, the evaluation of the potential impact of the various mixtures on the environment is complicated.

PCBs are highly lipophilic and bioconcentrate to high concentrations in tissue from concentrations in water that are often below the usual detection limits. When an evaluation of the impact of PCBs on the environment is performed, it is necessary to relate the data gathered in laboratory experiments with relatively pure mixtures to what happens to the mixtures in nature. There is evidence that percentages of chlorine change with time and location as the mixtures are transported through the environment. For example, the proportion of major peaks of Aroclor® 1254 in shrimp and fish captured from Escambia Bay, Florida, differed from each other (Nimmo, et al. 1971). The major peaks in these organisms and in organisms from laboratory studies (Hansen, et al. 1971) also differed from the standard used to calculate the amounts of the chemical in tissues. Results of environmental monitoring by Butler and Schultzmann (1978) showed that PCBs identified in fishes, Pacific staghorn sculpin and English sole from the Duwamish River in the state of Washington, during the period of fall 1972 to spring 1976, changed from those resembling Aroclor® 1254 to those resembling Aroclor® 1260 and, later, Aroclor® 1242.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

EFFECTS

Acute Toxicity

The acute toxicity data base for freshwater invertebrate species contains 12 values for three species. These values were from both static and flow-through tests; the flow-through tests showed an LC_{50} range from 10 μg/l for scud, *Gammarus fasciatus*, to 400 μg/l for the damselfly, *Ischnura verticalis*.

Six 96-hour LC_{50} values (Table 1) are available for four freshwater fish species; all of these are from flow-through tests with measured concentrations. Newly hatched rainbow trout were the most sensitive species tested, with a 96-hour LC_{50} of 2.0 μg/l for Capacitor® 21 (21 percent chlorine); largemouth bass were almost equally sensitive with a 96-hour

LC_{50} of 2.3 μg/l (Birge, et al. 1979). The fathead minnow had a similar LC_{50} of 7.7 μg/l for Aroclor® 1254 (Nebeker, et al. 1974). All of the acute values for fish species are for newly hatched fishes, reflecting their much greater sensitivity as compared to the other fish life stages.

The toxicity of PCBs appears to be similar for both fish and invertebrate freshwater species if test methods are considered. The lowest species mean acute value is 2.0 μg/l for rainbow trout (Table 3).

The LC_{50} or EC_{50} values for saltwater invertebrate species range from 10.2 to 60 μg/l (Table 1). The available data show little difference in the acute toxicity of different Aroclors®. This low variability in species sensitivity and small difference in acute toxicity of the Aroclors® tested could be real. However, it is likely that this is a function of the small number of species tested and that the solubilities of PCBs are less than their acute toxicities.

Acute toxicity tests of PCB mixtures to saltwater fish species have not produced data that can be used to obtain 96-hour LC_{50} values because concentrations tested were not sufficiently high (Table 6). Pinfish were not affected in 48 hours by 100 μg/l Aroclor® 1254 (Duke, et al. 1970). Eighteen percent of the pinfish died after 96 hours in water to which 100 μg/l Aroclor® 1016 was added, compared to 2 percent of the control fish, (Hansen, et al. 1974a). Additional tests with saltwater fish species at slightly higher concentrations might have given data sufficient to calculate 96-hour LC_{50} values. However, possible problems could exist in validity of acute tests with PCBs because of their low solubility in water (Schoor, 1975; Wiese and Griffin, 1978).

There are too few data for PCBs and freshwater or saltwater species to calculate a Freshwater or Saltwater Final Acute Value according to the procedures described in the Guidelines. Species mean acute values are summarized in Table 3.

Chronic Toxicity

Results from six chronic tests with three freshwater invertebrate species, *Daphnia magna*, *Gammarus pseudolimnaeus*, and the midge, *Tanytarsus dissimilis*, are shown in Table 2. The chronic values for *Daphnia magna* of 4.3 µg/l for Aroclor® 1248 and 2.1 µg/l for Aroclor® 1254, were from flow-through tests with measured concentrations (Nebeker and Puglisi, 1974). The value of 0.8 µg/l for the midge with Aroclor® 1254, and the two chronic values of 4.9 µg/l for Aroclor® 1242 and 3.3 µg/l for Aroclor® 1248 for *Gammarus pseudolimnaeus*, were also from flow-through tests with measured concentrations.

Five freshwater flow-through tests with measured concentrations have been conducted with two fish species, four with fathead minnows and one with brook trout (Table 2). The most toxic Aroclor® to fathead minnows was Aroclor® 1248 which gave a chronic value of 0.2 µg/l (Defoe, et al. 1978); chronic values for Aroclor® 1242, Aroclor® 1254, and Aroclor® 1260 were 9.0, 2.9, and 2.3 µg/l, respectively (Nebeker, et al. 1974; DeFoe, et al. 1978). A chronic value of 1.0 µg/l for Aroclor® 1254 was obtained by Mauck, et al. (1978) for the brook trout.

Two geometric mean acute-chronic ratios are calculable; these are 6.4 for the fathead minnow and 11 for the scud, *Gammarus pseudolimnaeus* (Table 2).

No chronic tests have been reported in which saltwater invertebrate species were exposed to PCBs.

In an early-life-stage test (Table 2) with the sheepshead minnow, fertilization was not affected by Aroclor® 1254, but significantly fewer embryos survived to hatching in a measured concentration of 3.48 µg/l (Schimmel, et al. 1974). Survival of fish during the two weeks following hatching was significantly less in 0.16 µg/l, but not different from controls in 0.06 µg/l.

In a study to determine the effect of PCBs in fish embryos on survival, Hansen, et al. (1973) exposed adult sheepshead minnows for four weeks to Aroclor® 1254 (Table 6). Adult fish exposed to 5.6 µg/l died, but those in 1.1 µg/l or lower apparently were not affected. Embryos from adult fish exposed to concentrations as low as 0.14 µg/l were placed in PCB-free flowing saltwater and observed for four weeks. Fertilization success was not affected by PCBs in embryos, but survival of embryos and the resulting fry was reduced (Table 6). Fry from embryos containing 7.0 µg/g or more of PCB began dying a few hours after hatching. The concentration in embryos calculated to be lethal to 50 percent of the fish was 6.1 µg/g. If PCB affects other species similarly, then other fish species with equally high concentrations of Aroclor® 1254 in their embryos may be endangered.

The effect of another PCB, Aroclor® 1016, in water on fry, juvenile, or adult sheepshead minnows was determined in a 4-week exposure (Hansen, et al. 1975)(Table 2). Survival of all three life stages was reduced in 15 µg/l but not in 3.4 µg/l or less. Unlike Aroclor® 1254, as much as 77 µg/g of Aroclor® 1016 in embryos apparently did not affect survival of embryos and fry in water free of this PCB.

Concentrations of Aroclor® 1016 and 1254 affecting sheepshead minnows in chronic exposures differed markedly (7.14 and 0.098 µg/l); similarly, life-cycle tests with the fathead minnow and Aroclors® 1242, 1248, 1254, and 1260 yielded chronic values of 0.2 to 9.0 µg/l (Table 2). Degree of chlorination in these tests using a freshwater fish species appears unrelated to extent of chronic toxicity and suggests that additional chronic data on saltwater species for other Aroclors® may be needed to demonstrate adequately the presence of a relationship between degree of chlorination and chronic toxicity.

Chronic exposure of saltwater fish species to Aroclors® produced pathological effects not observed in acute tests. Hansen, et al. (1971) reported signs of poisoning in pinfish exposed to 5 µg/l Aroclor® 1254, such as fungus-like lesions on the body, hemorrhagic areas around the mouth, ragged fins etc.; and 41 to 66 percent mortality occurred. Signs of poisoning in adult sheepshead minnows exposed to 10 µg/l Aroclor® 1254 and juvenile sheepshead minnows exposed to 0.16 µg/l or greater included lethargy, fin rot, and reduced feeding (Hansen, et al. 1973; Schimmel, et al. 1974); decreased survival occurred at concentrations where these signs of poisoning were observed (Table 6).

Spot exposed to 5 µg/l Aroclor® 1254 for two weeks or longer showed fatty changes in their livers (Nimmo, et al. 1975). In intermediate stages of liver pathogenesis in fish species exposed to Aroclor® 1254, there were extreme fatty changes characterized by the presence of large vacuoles within hepatocytes and disorientation of liver cord distribution. In advanced stages of pathogenesis in moribund fish, there were intracellular PAS-positive bodies (ceroid), congestion of blood sinuses, and severe vacuolation (Table 6).

Chronic toxicity tests, including early-life-stage tests with fishes, demonstrate that the toxicity of PCBs increases with increased duration of exposure. Because data on the acute toxicity of PCBs to saltwater organisms are limited, the relationship between acute and chronic toxicity is poorly understood. Available data (Tables 2 and 6) from chronic tests demonstrate that Aroclor® 1254 affects saltwater organisms at concentrations as low as 0.14 µg/l and Aroclor® 1016 affects pinfish at 15 µg/l. No effects have been observed at 0.06 µg/l for Aroclor® 1254 and at 3.4 µg/l for Aroclor® 1016.

Plant Effects

No appropriate freshwater plant effects data are available, but information which has been found for plants is given in Table 6. Information concerning the sensitivity of saltwater plant species is restricted to unicellular algae (Table 4). Fisher and Wurster (1973) found that the growth of the diatom, *Rhizosolenia setigera*, was reduced in a medium to which 0.1 µg/l Aroclor® 1254 was added. Likewise, Fisher, et al. (1974) demonstrated that 0.1 µg/l Aroclor® 1254 added per liter of water changed the species ratio of the alga, *Dunaliella tertiolecta*, and the diatom, *Thalassiosira pseudonana*. Fisher, et al. (1974) also showed a decrease in species diversity and species ratio change in natural phytoplankton communities at 0.1 µg/l Aroclor® 1254. In summary, some data suggest that unicellular plants are affected by concentrations of PCBs similar to concentrations that are chronically toxic to animals. Unfortunately, no data using measured concentrations were presented, and it is difficult to interpret the ecological significance of these studies.

Residues

Table 5 contains the results of 21 appropriate freshwater residue studies as defined by the Guidelines. The studies include only laboratory data for invertebrate and fish species and show a wide range of bioconcentration factors (BCF). Freshwater field studies were placed in Table 6 rather than Table 5 because it could not be shown that the PCB concentration in water was constant for a long period of time over the range of territory inhabited by the organism. Freshwater invertebrate BCF values in Table 5 range from 2,700 for the phantom midge exposed for 14 days to 108,000 for the scud, *Gammarus pseudolimnaeus*, exposed for 60 days. BCF values for exposures of fish species (Table 5) range from 3,000 for brook trout (fillets) exposed to Aroclor® 1254 for 500 days to 274,000 for fathead minnows (whole body) exposed to Aroclor® 1242 for 255 days.

The BCF values of PCBs in saltwater species in laboratory tests are also shown in Table 5. The diatom, *Cylindrotheca closterium*, had a BCF of 1,000 (Keil, et al. 1971); Eastern oyster, up to 101,000 (Lowe, et al. 1972; Parrish, et al. 1974); grass shrimp, *Palaemonetes pugio*, 27,000 (Nimmo, et al. 1974); and in the three fish species listed, *Leiostomus xanthurus*, *Cyprinodon variegatus*, and *Lagodon rhomboides*, as high as 43,100 (Hansen, et al. 1971, 1973, 1974a, 1975). Bioconcentration factors for PCBs in five of six species of freshwater fishes in laboratory tests were generally similar to BCF values for saltwater species. Variation in BCF values among species is greater than the variation in BCF values when one species is exposed to various Aroclors®. For example, BCF values in adult sheepshead minnows exposed under similar conditions averaged 25,000 for Aroclor® 1016 and 30,000 for Aroclor® 1254.

Bioconcentration factors calculated from data from Escambia Bay, Florida, were greater than 230,000 for blue crab, greater than 100,000 for oysters, and greater than 670,000 for speckled trout (Duke, et al. 1970; Nimmo, et al. 1975). These data, and field data on freshwater fish species, suggest that either BCF from laboratory studies underestimate bioconcentration potentials of PCBs in the environment or that water samples from field studies inadequately characterized ambient concentrations of PCBs (Hansen, 1975).

The bioaccumulation of PCBs into aquatic organisms from PCBs in food and in water and the effects of PCBs on mammals that feed on fish and shellfish are important. The lowest maximum permissible tissue concentration (0.64 µg/l) is based on the effect of dietary PCBs on mink (Platonow and Karstad, 1973). Significant effects on reproduction of mink were observed at this concentration but a safe concentration was not determined.

Dividing a BCF value by the percent lipid value for the same species provides a BCF value based on 1 percent lipid content; this resultant BCF value is referred to as the normalized BCF. Each of the BCF values for which percent lipid data are available was normalized by dividing the BCF value by its corresponding percent lipid value. The geometric mean of the normalized BCF values was then calculated to be 10,400 (Table 5). The action level for marketability for human consumption established by the U.S. Food and Drug Administration (FDA) for PCBs in edible fish and shellfish is 5.0 mg/kg. Dividing the FDA action level of 5.0 mg/kg by the geometric mean of normalized BCF values (10,400) and by a percent lipid value of 15 for freshwater species (see Guidelines) gives a freshwater residue value of 0.032 µg/l. Similarly, dividing the FDA action level of 5.0 mg/kg by the geometric mean of normalized BCF values (10,400), and by a percent lipid value of 16 for saltwater species (see Guidelines) gives a saltwater residue value of 0.030 µg/l. The highest BCF value for edible portion of a consumed freshwater species is 9,550 for rainbow trout (Branson, et al. 1975). Dividing this value into the FDA action level of 5.0 mg/kg gives a freshwater residue value of 0.52 µg/l. The highest BCF value for edible portion of a consumed saltwater species is the value of 101,000 for Eastern oyster (Lowe, et al. 1972). Dividing this value into the FDA action level of 5.0 mg/kg gives a saltwater residue value of 0.050 µg/l. These concentrations are probably too high because the average concentration in some edible species would be at the FDA action level.

For wildlife protection, the lowest maximum permissible tissue concentration is 0.64 mg/kg for mink (Plantonow and Karstad, 1973), but this level adversely affected mink. Dividing this value by the geometric mean (45,000) of whole-body BCF values for salmonids (rainbow trout, 46,000; brook trout, 42,000 and 47,000) gives a residual value for freshwater of 0.014 µg/l. The mean BCF of 45,000 for salmonids is based only on laboratory data. Eleven BCF values for salmonids are available from field studies (Table 6). The highest is for the siscowet, but the other 10 range from 119,000 to 2,333,000 with a geometric mean of 456,000. Even if the concentrations of PCBs in water in these field studies are not documented as well as desired, the total available information strongly indicates that field BCF values for PCBs are probably a factor at 10 higher than the available laboratory BCF values. The data from Escambia Bay indicate that similar effects occur with saltwater fishes (Table 5). The model developed by Weiniger (1978) provides a possible explanation for this difference between laboratory and field data. Thus the freshwater and saltwater Final Residue Values of 0.014 and 0.030 µg/l, respectively, are probably at least a factor of 10 too high.

Miscellaneous

Table 6 contains data for other effects not listed in Tables 1 through 5. The tests conducted by Birge, et al. (1979) with Capacitor® 21 are flow-through early-life-stage tests with measured concentrations, where embryos were tested from just after fertilization until 4 days post-hatch (Table 6). Test LC_{50} values for redear sunfish were 8 µg/l; for largemouth bass 1.5 μg/l; and for rainbow trout 2.0 μg/l. These low values are very close to the data of Nebeker, et al. (1974) and Defoe, et al. (1978) for fathead minnows (Table 2).

Several studies have shown that tests for PCBs lasting longer than 96 hours (Table 6) provide a better estimate of long-term adverse effects (mortality, growth, pathology) than lethality in 96-hour tests. Aroclor® 1254 killed pink shrimp at a concentration of 0.94 μg/l within 15 days (Nimmo, et al. 1971). Pink shrimp exposed to 3.0 μg/l for 7 days were sensitive changes in salinity (Nimmo and Bahner, 1974). This species also appeared more susceptible to a viral infection after exposure to Aroclor® 1254 (Couch and Nimmo, 1974a,b).

The growth rate (height and in-water weight) of Eastern oysters was significantly reduced by exposure to 5.0 μg/l Aroclor® 1254 for 24 weeks (Lowe, et al. 1972). These oysters also displayed general tissue alterations in the vesilcular connective tissue (parenchyma) around the digestive diverticula of the hepatopancreas.

Aroclor® 1254 was toxic to the saltwater amphipod, Gammarus oceanicus, at a nominal concentration of 10.0 μg/l (Table 6). Molting animals were particularly vulnerable to the PCB. Necrotic branchia were found in some animals exposed for about 6 days to nominal concentration of 1.0 μg/l.

Aroclor® 1254 affected the species composition of communities of estuarine animals that developed from planktonic larvae in saltwater that flowed for four months through small aquaria (Table 6; Hansen, 1974). The number of arthropods decreased while the number of chordates increased in aquaria receiving 0.6 μg/l of the PCB. Numbers of phyla, species and individuals were decreased by this PCB, but there was no apparent effect on the abundance of annelids, brachiopods, coelenterates, echiniderms, or nemerteans. This study showed that a PCB can have marked effects on community structure at concentrations not much different from those that produced chronic effects on single species.

Summary

The acute toxicity of polychlorinated biphenyls (PCBs) to freshwater animals has been measured with three invertebrate and four fish species, and the species mean acute values range from 2.0 to 283 µg/l. The data from flow-through tests with measured concentrations are similar for fish and invertebrate species, and probably accurately reflect the toxicity of the compounds. The data from static tests are more variable, and many may not reflect actual toxicity, due to volatility, solubility, bioconcentration, and adsorption characteristics of the various PCB compounds. Eleven life-cycle or partial life-cycle tests were completed with three invertebrate and two fish species; the chronic values range from 0.2 to 15 µg/l.

Species mean acute values for PCBs and saltwater animals range from 10.5 to 20 µg/l from six tests on three invertebrate species. Two chronic tests have been conducted on the sheepshead minnow, providing chronic values for this species of 7.14 and 0.098 µg/l.

The freshwater residue data show that PCBs accumulate to relatively high levels in fish and invertebrate tissues, and that for most species PCBs are not rapidly depurated when exposure is discontinued. Bioconcentration factors for invertebrate species range from 2,700 to 108,000. Bioconcentration factors for PCB exposures of fish species range from 3,000 to 274,000.

Bioconcentration data for PCBs in saltwater fish and invertebrate species show bioconcentration factors ranging from 800 to >230,000 for invertebrate species and from 14,400 to >670,000 for fish species.

The BCF values obtained from field data are generally apreciably higher than laboratory-derived BCF values, so Final Residue Values based on laboratory-derived BCF values are probably at least a factor of 10 too high.

Data available for freshwater plant species generally indicate that they are less sensitive to PCBs than are invertebrates or fish species. Data available for saltwater plant species indicate that unicellular plants are affected by concentrations of PCBs similar to concentrations that are chronically toxic to animals.

CRITERIA

For polychlorinated biphenyls the criterion to protect freshwater aquatic life as derived using the Guidelines is 0.014 µg/l as a 24-hour average. The concentration of 0.014 µg/l is probably too high because it is based on bioconcentration factors measured in laboratory studies, but field studies apparently produce factors at least 10 times higher for fishes. The available data indicate that acute toxicity to freshwater aquatic life probably will only occur at concentrations above 2.0 µg/l and that the 24-hour average, should provide adequate protection aganist acute toxicity.

For polychlorinated biphenyls the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.030 µg/l as a 24-hour average. The concentration at 0.030 µg/l is probably too high because it is based on bioconcentration factors measured in laboratory studies, but field studies apparently produce factors at least 10 times higher for fishes. The available data indicate that acute toxicity to saltwater aquatic life probably will only occur at concentrations above 10 µg/l and that the 24-hour average should provide adequate protection against acute toxicity.

Table 1. Acute values for polychlorinated biphenyls

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		FRESHWATER SPECIES			
Scud, *Gammarus fasciatus*	FT, M	Aroclor® 1242	10	-	Mayer, et al. 1977
Scud, *Gammarus fasciatus*	S, U	Aroclor® 1248	52	-	Mayer, et al. 1977
Scud, *Gammarus fasciatus*	S, U	Aroclor® 1254	2,400	10	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	FT, M	Aroclor® 1242	73	-	Nebeker & Puglisi, 1974
Scud, *Gammarus pseudolimnaeus*	FT, M	Aroclor® 1248	29	-	Nebeker & Puglisi, 1974
Scud, *Gammarus pseudolimnaeus*	S, U	2,3,4'-trichlorobiphenyl	70	-	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	S, U	4,4'-dichlorobiphenyl	100	-	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	S, U	2,4'-dichlorobiphenyl	120	-	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	S, U	2,4,6,2',4',6'-hexachlorobiphenyl	150	-	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	S, U	2,4,5,2',5'-pentachlorobiphenyl	210	46	Mayer, et al. 1977
Damselfly, *Ischnura verticalis*	FT, M	Aroclor® 1254	200	-	Mayer, et al. 1977
Damselfly, *Ischnura verticalis*	FT, M	Aroclor® 1242	400	283	Mayer, et al. 1977
Rainbow trout, *Salmo gairdneri*	FT, M	Capacitor® 21	2.0	2	Birge, et al. 1979
Fathead minnow, *Pimephales promelas*	FT, M	Aroclor® 1242	15	-	Nebeker, et al. 1974

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
Fathead minnow (juvenile), *Pimephales promelas*	FT, M	Aroclor® 1242	300	-	Nebeker, et al. 1974
Fathead minnow, *Pimephales promelas*	FT, M	Aroclor® 1254	7.7	33	Nebeker, et al. 1974
Redear sunfish, *Lepomis microlophus*	FT, M	Capacitor® 21	19	19	Birge, et al. 1979
Largemouth bass, *Micropterus salmoides*	FT, M	Capacitor® 21	2.3	2.3	Birge, et al. 1979
SALTWATER SPECIES					
Eastern oyster, *Crassostrea virginica*	FT, U	Aroclor® 1016	10.2**	-	Hansen, et al. 1974a
Eastern oyster, *Crassostrea virginica*	FT, U	Aroclor® 1248	17**	-	Lowe, undated
Eastern oyster, *Crassostrea virginica*	FT, U	Aroclor® 1254	14**	-	Lowe, undated
Eastern oyster, *Crassostrea virginica*	FT, U	Aroclor® 1260	60**	20	Lowe, undated
Brown shrimp, *Penaeus aztecus*	FT, U	Aroclor® 1016	10.5	10.5	Hansen, et al. 1974a
Grass shrimp, *Palaemonetes pugio*	FT, U	Aroclor® 1016	12.5	12.5	Hansen, et al. 1974a

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* S = static, FT = flow-through, U = unmeasured, M = measured

**EC50 based on decreased growth of oysters

Table 2. Chronic values for polychlorinated biphenyls

Species	Test*	Chemical	Limits (µg/l)	Chronic Value (µg/l)	Reference
		FRESHWATER SPECIES			
Cladoceran, *Daphnia magna*	LC	Aroclor® 1254	10-24	15	Maki & Johnson, 1975
Cladoceran, *Daphnia magna*	LC	Aroclor® 1248	2.5-7.5	4.3	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	LC	Aroclor® 1254	1.2-3.5	2.1	Nebeker & Puglisi, 1974
Scud, *Gammarus pseudolimnaeus*	LC	Aroclor® 1242	2.8-8.7	4.9	Nebeker & Puglisi, 1974
Scud, *Gammarus pseudolimnaeus*	LC	Aroclor® 1248	2.2-5.1	3.3	Nebeker & Puglisi, 1974
Midge, *Tanytarsus dissimilis*	LC	Aroclor® 1254	0.5-1.2	0.8	Nebeker & Puglisi, 1974
Brook trout, *Salvelinus fontinalis*	LC	Aroclor® 1254	0.7-1.5	1.0	Mauck, et al. 1978
Fathead minnow, *Pimephales promelas*	LC	Aroclor® 1248	0.1-0.4	0.2	DeFoe, et al. 1978
Fathead minnow, *Pimephales promelas*	LC	Aroclor® 1260	1.3-4.0	2.3	DeFoe, et al. 1978
Fathead minnow, *Pimephales promelas*	LC	Aroclor® 1242	5.4-15.0	9.0	Nebeker, et al. 1974
Fathead minnow, *Pimephales promelas*	LC	Aroclor® 1254	1.8-4.6	2.9	Nebeker, et al. 1974
		SALTWATER SPECIES			
Sheepshead minnow, *Cyprinodon variegatus*	ELS	Aroclor® 1016	3.4-15.0	7.14	Hansen, et al. 1975

Table 2. (Continued)

Species	Test*	Chemical	Limits (µg/l)	Chronic Value (µg/l)	Reference
Sheepshead minnow, *Cyprinodon variegatus*	ELS	Aroclor® 1254	0.06-0.16	0.098	Schimmel, et al. 1974

* LC = life cycle or partial life cycle, ELS = early life stage

Acute-Chronic Ratios

Species	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Scud, *Gammarus pseudolimnaeus*	46	4.9	9.4
Scud, *Gammarus pseudolimnaeus*	46	3.3	14
Fathead minnow, *Pimephales promelas*	33	9.0	3.7
Fathead minnow, *Pimephales promelas*	33	2.9	11

Geometric mean of acute-chronic ratios for scuds = 11

Geometric mean of acute-chronic ratios for fathead minnows = 6.4

Table 3. Species mean acute values and acute-chronic ratios for polychlorinated biphenyls

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
	FRESHWATER SPECIES		
7	Damselfly, *Ischnura verticalis*	283	-
6	Scud, *Gammarus pseudolimnaeus*	46	11
5	Fathead minnow, *Pimephales promelas*	33	6.4
4	Redear sunfish, *Lepomis microlopus*	19	-
3	Scud, *Gammarus fasciatus*	10	-
2	Largemouth bass, *Micropterus salmoides*	2.3	-
1	Rainbow trout, *Salmo gairdneri*	2.0	-
	SALTWATER SPECIES		
3	Eastern oyster, *Crassostrea virginica*	20	-
2	Grass shrimp, *Palaemonetes pugio*	12.5	-
1	Brown shrimp, *Penaeus aztecus*	10.5	-

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* Ranked from least sensitive to most sensitive based on species mean acute value.

Table 4. Plant values for polychlorinated biphenyls

Species	Chemical	Effect	Result (µg/l)	Reference
		SALTWATER SPECIES		
Diatom, *Rhizosolenia setiger*	Aroclor® 1254	No growth in 48 hr. Reduced growth thereafter	0.1	Fisher & Wurster, 1973
Diatom, *Thalassiosira pseudonana*	Aroclor® 1254	Reduced growth	25 to 100	Mosser, et al. 1972a
Diatom, *Thalassiosira pseudonana*	Aroclor® 1254	Reduced cell division	1.0	Harding & Phillips, 1978
Diatoms, *Thalassiosira pseudonana* and *Skeletonema costatum*	Aroclor® 1254	Reduced growth and carbon fixation in 48 hr	10	Fisher, 1975
Diatom, *Thalassiosira pseudonana* and green alga, *Dunaliella tertiolecta*	Aroclor® 1254	Species ratio change	1	Mosser, et al. 1972b
Diatom, *Thalassiosira pseudonana* and green alga, *Dunaliella tertiolecta*	Aroclor® 1254	Species ratio change	0.1	Fisher, et al. 1974
Diatom, *Skeletonema costatum*	Aroclor® 1254	Reduced growth	10	Mosser, et al. 1972a
Diatom, *Skeletonema costatum*	Aroclor® 1254	Reduced cell division	10	Harding & Phillips, 1978
Diatom, *Cylindrotheca closterium*	Aroclor® 1254	Reduced growth	100	Keil, et al. 1971
Diatom, *Chaetoceros socialis*	Aroclor® 1254	Reduced cell division	10	Harding & Phillips, 1978
Diatom, *Nitzschia longissima*	Aroclor® 1254	No effect on cell division	100	Harding & Phillips, 1978
Chrysophyceae, *Monochrysis lutheri*	Aroclor® 1254	Reduced cell division	10	Harding & Phillips, 1978

Table 4. (Continued)

Species	Chemical	Effect	Result (µg/l)	Reference
Haptophyceae, *Isochrysis galbana*	Aroclor® 1254	Reduced cell division	1	Harding & Phillips, 1978
Chlorophyceae, *Dunaliella tertiolecta*	Aroclor® 1254	Increased cell division	100	Harding & Phillips, 1978
Phytoplankton populations	Aroclor® 1254	Toxicity in 24 hrs	15	Moore & Harriss, 1972
Phytoplankton populations	Aroclor® 1242	Toxicity in 24 hrs	6.5	Moore & Harriss, 1972
Natural phytoplankton community	Aroclor® 1254	Decreased diversity, species ratio altered	100	Laird, 1973
Phytoplankton communities	Aroclor® 1254	Reduced biomass and size	1	O'Connors, et al. 1978

Table 5. Residues for polychlorinated biphenyls

Species	Tissue	Lipid (%)	Chemical	Bioconcentration Factor	Duration (days)	Reference
			FRESHWATER SPECIES			
Snail, *Physa* sp.	Whole body	-	Pentachloro-biphenyl	56,900	33	Sanborn, 1974
Cladoceran, *Daphnia magna*	Whole body	-	Aroclor® 1254	3,800	4	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	Whole body	-	Aroclor® 1242	36,000	60	Nebeker & Puglisi, 1974
Scud, *Gammarus pseudolimnaeus*	Whole body	-	Aroclor® 1254	6,200	21	Mayer, et al. 1977
Scud, *Gammarus pseudolimnaeus*	Whole body	-	Aroclor® 1248	108,000	60	Nebeker & Puglisi, 1974
Mosquito, *Culex tarsalis*	Whole body	-	Aroclor® 1254	3,500	7	Mayer, et al. 1977
Phantom midge, *Chaoborus punctipennis*	Whole body	-	Aroclor® 1254	2,700	14	Mayer, et al. 1977
Rainbow trout, *Salmo gairdneri*	Whole body	-	Aroclor® 1254	46,000	30	Bills & Marking, 1977
Rainbow trout, *Salmo gairdneri*	Fillet	-	Tetrachloro-biphenyl	9,550	estimated plateau	Branson, et al. 1975
Rainbow trout, *Salmo gairdneri*	Fillet	-	Tetrachloro-biphenyl	5,850	42	Branson, et al. 1975
Brook trout, *Salvelinus fontinalis*	Whole body	-	Aroclor® 1254	47,000	118	Mauck, et al. 1978
Brook trout, *Salvelinus fontinalis*	Whole body	2.9	Aroclor® 1254	42,000	500	Snarski & Puglisi, 1976
Brook trout, *Salvelinus fontinalis*	Fillet	0.7	Aroclor® 1254	3,000	500	Snarski & Puglisi, 1976
Fathead minnow (female), *Pimephales promelas*	Whole body	-	Aroclor® 1248	120,000	240	DeFoe, et al. 1978

Table 5. (Continued)

Species	Tissue	Lipid (%)	Chemical	Bioconcentration Factor	Duration (days)	Reference
Fathead minnow (female), *Pimephales promelas*	Whole body	-	Aroclor® 1260	270,000	240	DeFoe, et al. 1978
Fathead minnow (male), *Pimephales promelas*	Whole body	-	Aroclor® 1242	274,000	255	Nebeker, et al. 1974
Fathead minnow (female), *Pimephales promelas*	Whole body	-	Aroclor® 1254	238,000	240	Nebeker, et al. 1974
White sucker, *Catostomus commersoni*	Whole body	-	Aroclor® 1232	5,500	30	Frederick, 1975
Channel catfish, *Ictalurus punctatus*	Whole body	-	Aroclor® 1254	61,200	77	Mayer, et al. 1977
Channel catfish, *Ictalurus punctatus*	Whole body	-	Aroclor® 1248	56,400	77	Mayer, et al. 1977
Bluegill, *Lepomis macrochirus*	Whole body	-	Aroclor® 1248	52,000	77	Stalling, 1971
			SALTWATER SPECIES			
Diatom, *Cylindrotheca closterium*	Whole organism	-	Aroclor® 1242	1,000	14	Keil, et al. 1971
Polychaete, *Nereis diversicolor*	Whole body	-	Phenochlor® DP-5	800	14	Fowler, et al. 1978
Eastern oyster, *Crassostrea virginica*	Edible portion	-	Aroclor® 1016	13,000	84	Parrish, et al. 1974
Eastern oyster, *Crassostrea virginica*	Edible portion	-	Aroclor® 1254	101,000	245	Lowe, et al. 1972
Eastern oyster, *Crassostrea virginica*	Edible portion	-	Aroclor® 1254	>100,000	Field data	Duke, et al. 1970; Nimmo, et al. 1975
Grass shrimp, *Palaemonetes pugio*	Whole body	-	Aroclor® 1254	27,000	16	Nimmo, et al. 1974
Blue crab, *Callinectes sapidus*	Whole body	-	Aroclor® 1254	>230,000	Field data	Nimmo, et al. 1975

Table 5. (Continued)

Species	Tissue	Lipid (%)	Chemical	Bioconcentration Factor	Duration (days)	Reference
Spot, *Leiostomus xanthurus*	Whole body	1.1*	Aroclor® 1254	37,000	28	Hansen, et al. 1971
Sheepshead minnow (adult), *Cyprinodon variegatus*	Whole body	3.6*	Aroclor® 1016	25,000	28	Hansen, et al. 1975
Sheepshead minnow (juvenile), *Cyprinodon variegatus*	Whole body	-	Aroclor® 1016	43,100	28	Hansen, et al. 1975
Sheepshead minnow (fry), *Cyprinodon variegatus*	Whole body	-	Aroclor® 1016	14,400	28	Hansen, et al. 1975
Sheepshead minnow (adult), *Cyprinodon variegatus*	Whole body	3.6*	Aroclor® 1254	30,000	28	Hansen, et al. 1973
Pinfish, *Lagodon rhomboides*	Whole body	-	Aroclor® 1016	17,000	21-28	Hansen, et al. 1974a
Speckled trout, *Cynoscion nebulosus*	Whole body	-	Aroclor® 1254	>670,000	Field data	Duke, et al. 1970; Nimmo, et al. 1975
Fishes	Whole body	-	Aroclor® 1254	>133,000**	Field data	Nimmo, et al. 1975
Invertebrates	Whole body	-	Aroclor® 1254	>27,000**	Field data	Nimmo, et al. 1975

* Percent lipid data from Hansen, 1980

** Greatest bioconcentration factor of Aroclor® 1254 in fishes and invertebrates, respectively from Escambia Bay, Florida

Maximum Permissible Tissue Concentration

Action Level or Effect	Concentration (mg/kg)	Reference
Fish and shellfish	5.0	U.S. FDA, 21 CFR Part 109.30
No reproduction and mortality in mink, *Mustela vison*	0.64	Platonow & Karstad, 1973

Table 5. (Continued)

Maximum Permissible Tissue Concentration

Action Level or Effect	Concentration (mg/kg)	Reference
Reduced survival of sheepshead minnow, *Cyprinodon variegatus*, from embryos containing ≥ 7.0 mg/kg	7.0	Hansen, et al. 1973

Geometric mean of normalized BCF values (see text) = 10,400

Marketability for human consumption: FDA action level for fish and shellfish = 5.0 mg/kg

Percent lipid values for freshwater species (see Guidelines) = 15

Percent lipid value for saltwater species (see Guidelines) = 16

Freshwater: $\frac{5.0}{10{,}400 \times 15} = 0.000032$ mg/kg = 0.032 µg/l

Saltwater: $\frac{5.0}{10{,}400 \times 16} = 0.000030$ mg/kg = 0.030 µg/l

Using highest BCF for edible portion of a consumed species

Freshwater: Rainbow trout = 9,550 (Branson, et al. 1975)

$\frac{5.0}{9{,}550} = 0.00052$ mg/kg = 0.52 µg/l

Saltwater: Eastern oyster = 101,000 (Lowe, et al. 1972)

$\frac{5.0}{101{,}000} = 0.000050$ mg/kg = 0.050 µg/l

Table 5. (Continued)

Wildlife protection: Lowest maximum permissible tissue concentration = 0.64 mg/kg (Platonow and Karstad, 1973)

Geometric mean of whole body BCF values for salmonid species = 45,000

Freshwater: $\frac{0.64}{45,000}$ = 0.000014 mg/kg = 0.014 µg/l

Freshwater Final Residue Value = 0.014 µg/l

Saltwater Final Residue Value = 0.030 µg/l

Table 6. Other data for polychlorinated biphenyls

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES			
Yeast, *Saccharomyces cerevisiae*	Aroclor® 1232 to Aroclor® 1260	160 hrs	Reduced growth	25,000	Tejedor, et al. 1979
Alga, *Euglena gracilis*	Aroclor® 1221	48 hrs	ID50	4,400	Ewald, et al. 1976
Alga, *Euglena gracilis*	Aroclor® 1242	8 days	Reduced growth	10,000	Bryan & Olafsson, 1978
Alga, *Scenedesmus obtusiusculus*	Aroclor® 1242	24 hrs	Growth inhibition	300	Larsson & Tillberg, 1975
Alga, *Scenedesmus quadricauda*	Aroclor® 1254	24 hrs	Reduction in rate of carbon fixation	0.1	Laird, 1973
Alga, *Chlorella pyrenoidosa*	Aroclor® 1268	191 hrs	Depressed cell productivity	1,000	Hawes, et al. 1976b
Alga, *Chlorella pyrenoidosa*	Aroclor® 1254	73 hrs	Reduced population growth	1,000	Hawes, et al. 1976a
Alga, *Chlamydomonas reinhardtii*	Aroclor® 1242	22 days	Reduced growth	2,000	Morgan, 1972
Alga, *Phormidium* sp.	Dichloro-biphenyl	3 hrs	Reduced motility	50	Zuliel & Benecke, 1978
Cladoceran, *Daphnia magna*	Aroclor® 1248	2 wks	LC50	2.6	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	Aroclor® 1254	2 wks	LC50	1.8	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	Aroclor® 1254	3 wks	LC50	1.3	Nebeker & Puglisi, 1974
Cladoceran, *Daphnia magna*	Aroclor® 1254	2 wks	LC50	24	Maki & Johnson, 1975
Cladoceran, *Daphnia magna*	Aroclor®1221 to Aroclor® 1260	2-3 wks	LC50	19-182	Nebeker & Puglisi, 1974

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Amphipod, *Pontiporeia affinis*	Field data	-	Bioconcentration factor = 1,709	-	Halle, et al. 1975
Stonefly, *Pteronarcys dorsata*	Aroclor® 1254	21 days	Bioconcentration factor = 740	-	Mayer, et al. 1977
Dobsonfly, *Corydalus cornutus*	Aroclor® 1254	7 days	Bioconcentration factor = 1,500	-	Mayer, et al. 1977
Mosquito, *Culex tarsalis*	Aroclor® 1254	7 days	No adult emergence	1.5	Sanders & Chandler, 1972
Glass shrimp, *Palaemonetes kadiakensis*	Aroclor® 1254	7 days	LC50	3	Mayer, et al. 1977
Glass shrimp, *Palaemonetes kadiakensis*	Field data	21 days	Bioconcentration factor = 2,600	-	Mayer, et al. 1977
Mysid, *Mysis relicta*	Field data	-	Bioconcentration factor = 125,000	-	Veith, et al. 1977
Snails	Field data	-	Bioconcentration factor = 45,000	-	Nadeau & Davis, 1976
Crayfish, *Orconectes nais*	Aroclor® 1242	7 days	LC50	30	Mayer, et al. 1977
Crayfish, *Orconectes nais*	Aroclor® 1254	21 days	Bioconcentration factor = 750	-	Mayer, et al. 1977
Rainbow trout, *Salmo gairdneri*	Aroclor® 1242 and Aroclor 1254	-	Inhibit ATPase activity	4 µg/g	Davis, et al. 1972
Rainbow trout, *Salmo gairdneri*	Aroclor® 1242	25 days	LC50	12	Mayer, et al. 1977

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Rainbow trout, *Salmo gairdneri*	Aroclor® 1248	25 days	LC50	3.4	Mayer, et al. 1977
Rainbow trout, *Salmo gairdneri*	Aroclor® 1254	25 days	LC50	27	Mayer, et al. 1977
Rainbow trout, *Salmo gairdneri*	Capacitor® 21	8 day early life stage	LC50	2	Birge, et al. 1979
Rainbow trout, *Salmo gairdneri*	Aroclor® 1260	25 days	LC50	49	Mayer, et al. 1977
Rainbow trout, *Salmo gairdneri*	Clophen® A-50	21 days	Induce fish heptic microsomal enzymes	31 µg/g	Lidman, et al. 1976
Rainbow trout, *Salmo gairdneri*	Aroclor® 1242	30 days	75% mortality, 70% deformed fry	0.39 µg/g	Hogan & Brauhn, 1975
Rainbow trout, *Salmo gairdneri*	Aroclor® 1254	330 days	Kidney pathology	10 µg/g	Nestel & Budd, 1974
Rainbow trout, *Salmo gairdneri*	Aroclor® 1242	5 days	LC50	67	Mayer, et al. 1977
Rainbow trout, *Salmo gairdneri*	Aroclor® 1254	5 days	LC50	54	Mayer, et al. 1977
Rainbow trout, *Salmo gairdneri*	Field data	-	Bioconcentration factor = 120,000	-	Veith, 1975
Steelhead trout, *Salmo gairdneri*	Aroclor® 1254	24 days	Bioconcentration factor = 38,000	-	Halter, 1974
Steelhead trout, *Salmo gairdneri*	Field data	-	Bioconcentration factor = 600,000	-	Hesse, 1973
Brown trout, *Salmo trutta*	Clophen® A-50	43 days	Anemia, hyperglycemia, altered cholesterol metabolism	10 µg/g in food	Johansson, et al. 1972

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Brown trout, *Salmo trutta*	Field data	-	Bioconcentration factor = 119,000	-	Veith, 1975
Atlantic salmon, *Salmo salar*	Aroclor® 1242	96 hrs	Bioconcentration factor = 600	-	Zitko & Carson, 1977
Atlantic salmon, *Salmo salar*	Aroclor® 1254	192 hrs	Mortality	>2 µg/g	Zitko, 1970
Coho salmon, *Oncorhynchus kisutch*	Aroclor® 1254	Early life stage	Chronic limit	<4.4	Halter & Johnson, 1974
Coho salmon, *Oncorhynchus kisutch*	Aroclor® 1254	72 hrs	Stimulated thyroid activity	0.48 µg/g	Mayer, et al. 1977
Coho salmon, *Oncorhynchus kisutch*	Aroclor® 1242	68 days	Induced fish hepatic AAH microsomal enzymes	1 µg/g	Gruger, et al. 1977
Coho salmon, *Oncorhynchus kisutch*	Pentachlorobiphenyl	72 days	Induction of aryl hydrocarbon hydroxylase	12 µg/g	Gruger, et al. 1976
Coho salmon, *Oncorhynchus kisutch*	Field data	-	Bioconcentration factor = 173,000	-	Veith, 1975
Chinook salmon, *Oncorhynchus tshawytscha*	Field data	-	Bioconcentration factor = 1,240,000	-	Hesse, 1973
Chinook salmon, *Oncorhynchus tshawytscha*	Field data	-	Bioconcentration factor = 240,000	-	Veith, 1975
Brook trout, *Salvelinus fontinalis*	Aroclor® 1254	18 days	Induced fish MFO system	39 µg/g	Addison, et al. 1978
Brook trout, *Salvelinus fontinalis*	Aroclor® 1254	71 wks	No effect on survival, growth or reproduction	0.94	Snarski & Puglisi, 1976
Brook trout, *Salvelinus fontinalis*	Aroclor® 1254	fert. to hatch	No embryo hatch	200	Freeman & Idler, 1975

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Lake trout, *Salvelinus namaycush*	Field data	-	Bioconcentration factor = 1,110,000	-	Hesse, 1973
Lake trout, *Salvelinus namaycush*	Field data	-	Bioconcentration factor = 212,000	-	Veith, 1975
Lake trout, *Salvelinus namaycush*	Field data	-	Bioconcentration factor = 2,333,000	-	Parejko, et al. 1975
Lake trout, *Salvelinus namaycush*	Field data	-	Bioconcentration factor = 1,625,000	-	Veith, et al. 1977
Siscowet, *Salvelinus namaycush siscowet*	Field data	-	Bioconcentration factor = 4,125,000	-	Veith, et al. 1977
Lake whitefish, *Coregonus clupeaformis*	Field data	-	Bioconcentration factor = 110,000	-	Hesse, 1973
Lake whitefish, *Coregonus clupeaformis*	Field data	-	Bioconcentration factor = 875,000	-	Veith, et al. 1977
Fathead minnow, *Pimephales promelas*	Aroclor® 1242	30 days	LC50	28	Veith, 1976
Fathead minnow, *Pimephales promelas*	Aroclor® 1016	30 days	LC50	28	Veith, 1976
Fathead minnow, *Pimephales promelas*	Aroclor® 1016	30 days	Reduced growth	23	Veith, 1976
Fathead minnow, *Pimephales promelas*	Aroclor® 1248	30 days	LC50	4.7	DeFoe, et al. 1978
Fathead minnow, *Pimephales promelas*	Aroclor® 1260	30 days	LC50	3.3	DeFoe, et al. 1978
Fathead minnow, *Pimephales promelas*	Aroclor® 1242	30 days	Significant mortality	23	Hermanutz & Puglisi, 1976
Fathead minnow, *Pimephales promelas*	Aroclor® 1016	30 days	Significant mortality	44	Hermanutz & Puglisi, 1976

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (μg/l)	Reference
Fathead minnow, *Pimephales promelas*	Aroclor® 1242	4 mos	Inhibition of ATPase activity	0.31	Cutkomp, et al. 1972
Fathead minnow, *Pimephales promelas*	Aroclor® 1254	4 mos	Inhibition of ATPase activity	0.31	Koch, et al. 1972
Bluegill, *Lepomis macrochirus*	Aroclor® 1248	5 days	LC50	136	Mayer, et al. 1977
Bluegill, *Lepomis macrochirus*	Aroclor® 1242	-	Inhibit (I50) ATPase	0.6 μg/g	Desaiah, et al. 1972
Bluegill, *Lepomis macrochirus*	Aroclor® 1254	-	Inhibition of ATPAse	30	Yap, et al. 1971
Bluegill, *Lepomis macrochirus*	Aroclor® 1242	30 days	LC50	84	Mayer, et al. 1977
Bluegill, *Lepomis macrochirus*	Aroclor® 1254	30 days	LC50	78	Mayer, et al. 1977
Bluegill, *Lepomis macrochirus*	Aroclor® 1254	30 days	LC50	177	Mayer, et al. 1977
Bluegill, *Lepomis macrochirus*	Aroclor® 1260	30 days	LC50	400	Mayer, et al. 1977
Mosquitofish, *Gambusia affinis*	Tri-, tetra-, & pentachloro-biphenyl	6 days	Bioconcentration factor = 12,000	-	Sanborn, 1974
Mosquitofish, *Gambusia affinis*	Aroclor® 1254	1.5 hr	Avoidance	0.1	Hansen, et al. 1974
Guppy, *Poecilia formosa*	Aroclor® 1242	1 day	Significant mortality	200	Morgan, 1972
Carp, *Cyprinus carpio*	Aroclor® 1248	20 days	Altered plasma -glucoronidase activity	5 μg/g	Ito, 1973

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Carp, *Cyprinus carpio*	Aroclor® 1248	21 days	Metabolic changes	250 µg/g	Ito & Murata, 1974
Carp, *Cyprinus carpio*	Field data	-	Bioconcentration factor = 110,000	-	Veith, 1975
Carp, *Cyprinus carpio*	Field data	-	Bioconcentration factor = 43,600	-	Hesse, 1973
Carp, *Cyprinus carpio*	Field data	-	Bioconcentration factor = 390,000	-	Hesse, 1973
Channel catfish, *Ictalurus punctatus*	Aroclor® 1248	30 days	LC50	75	Mayer, et al. 1977
Channel catfish, *Ictalurus punctatus*	Aroclor® 1254	30 days	LC50	139	Mayer, et al. 1977
Channel catfish, *Ictalurus punctatus*	Aroclor® 1254	72 hrs	Stimulated thyroid activity	2.4 µg/g	Mayer, et al. 1977
Channel catfish, *Ictalurus punctatus*	Aroclor® 1242	30 days	LC50	8.7	Mayer, et al. 1977
Channel catfish, *Ictalurus punctatus*	Aroclor® 1242	20 wks	Weight loss and liver hypertrophy	20 µg/g	Hansen, et al. 1976
Channel catfish, *Ictalurus punctatus*	Aroclor® 1254	2 wks	Increased transaminase, lower cortisol	8	Camp, et al. 1974
Flagfish, *Jordanella floridae*	Aroclor® 1242	30 days	Fin erosion	37	Hermanutz & Puglisi, 1976
Redear sunfish, *Lepomis microlophus*	Capacitor® 21	8 day early life stage	LC50	8	Birge, et al. 1979
Largemouth bass, *Micropterus salmoides*	Capacitor® 21	8 day early life stage	LC50	1.5	Birge, et al. 1979

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Largemouth bass, *Micropterus salmoides*	Field data	-	Bioconcentration factor = 3,500	-	Martell, et al. 1975
Gizzard shad, *Dorosoma cepedianum*	Field data	-	Bioconcentration factor = 150,300	-	Hesse, 1973
Alewife, *Alosa pseudoharengus*	Field data	-	Bioconcentration factor = 270,000	-	Hesse, 1973
Alewife, *Alosa pseudoharengus*	Field data	-	Bioconcentration factor = 89,000	-	Veith, 1975
Alewife, *Alosa pseudoharengus*	Field data	-	Bioconcentration factor = 42,700	-	Haile, et al. 1975
Chub, *Coregonus johannae*	Field data	-	Bioconcentration factor = 850,000	-	Hesse, 1973
Round whitefish (menominee), *Prosopium cylindaceum*	Field data	-	Bioconcentration factor = 120,000	-	Hesse, 1973
Common shiner, *Notropis cornutus*	Field data	-	Bioconcentration factor = >78,000	-	Nadeau & Davis, 1976
Longnose sucker, *Catostomus catostomus*	Field data	-	Bioconcentration factor = 150,000	-	Hesse, 1973
Longnose sucker, *Catostomus catostomus*	Field data	-	Bioconcentration factor = 1,125,000	-	Veith, et al. 1977
Redhorse sucker, *Moxostoma* sp.	Field data	-	Bioconcentration factor = 32,000	-	Veith, 1975
White sucker, *Catostomus commersoni*	Field data	-	Bioconcentration factor = 106,000	-	Veith, 1975
Burbot, *Lota lota*	Field data	-	Bioconcentration factor = 1,062,500	-	Veith, et al. 1977
Bloater, *Coregonus hoyi*	Field data	-	Bioconcentration factor = 1,166,200	-	Veith, et al. 1977

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Bloater, Coregonus hoyi	Field data	-	Bioconcentration factor = 81,000	-	Veith, et al. 1977
Lake herring, Coregonus artedii	Field data	-	Bioconcentration factor = 250,000	-	Veith, et al. 1977
Rainbow smelt, Osmerus mordax	Field data	-	Bioconcentration factor = 462,500	-	Veith, et al. 1977
Rainbow smelt, Osmerus mordax	Field data	-	Bioconcentration factor = 32,000	-	Veith, 1975
Rainbow smelt, Osmerus mordax	Field data	-	Bioconcentration factor = 48,000	-	Halie, et al. 1975
Rock bass, Ambloplites rupestris	Field data	-	Bioconcentration factor = 117,000	-	Nadeau & Davis, 1976
Pike, Esox lucius	Field data	-	Bioconcentration factor = 15,000	-	Hesse, 1973
Yellow perch, Perca flavescens	Field data	-	Bioconcentration factor = 50,000	-	Hesse, 1973
Yellow perch, Perca [illegible]avescens	Field data	-	Bioconcentration factor = 109,000	-	Veith, 1975
Yellow perch, Perca flavescens	Field data	-	Bioconcentration factor = 154,000	-	Norstrom, et al. 1976
Slimy sculpin, Cottus cognatus	Field data	-	Bioconcentration factor = 300,000	-	Veith, et al. 1977
Slimy sculpin, Cottus cognatus	Field data	-	Bioconcentration factor = 84,000	-	Halie, et al. 1975
Fourhorn sculpin, Myoxocephalus quadricornis	Field data	-	Bioconcentration factor = 337,500	-	Veith, et al. 1977
Mink, Mustela vison	Aroclor® 1254	-	Reduced reproduction	2 µg/g	Aulerich & Ringer, 1977

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Mink, *Mustela vison*	PCB residues	1 yr	Depressed growth	10 µg/g	Aulerich, et al. 1973
Mink, *Mustela vison*	Aroclor® 1254	4 mos	Reduced reproduction	1.0 µg/g	Ringer, et al. 1972
		SALTWATER SPECIES			
Chlorophyceae, *Dunaliella* sp.	Aroclor® 1254	45 days	Bioconcentration factor = 477,000 in lipid and 30,000 in dry tissue	-	Scura & Theilacker, 1977
Ciliate protozoans, *Tetrahymena pyriformis*	Aroclor® 1254	7 days	Bioconcentration factor = 60	-	Cooley, et al. 1972
Ciliate protozoans, *Tetrahymena pyriformis*	Aroclor® 1248	96 hrs	Reduced growth	1,000	Cooley, et al. 1973
Ciliate protozoans, *Tetrahymena pyriformis*	Aroclor® 1254	96 hrs	Reduced growth	1.0	Cooley, et al. 1972
Ciliate protozoans, *Tetrahymena pyriformis*	Aroclor® 1260	96 hrs	Reduced growth	1,000	Cooley, et al. 1973
Polychaete, *Arenicola marina*	Aroclor® 1254	5 days	Bioconcentration factor = 236	-	Courtney & Langston, 1978
Polychaete, *Nereis diversicolor*	Aroclor® 1254	5 days	Bioconcentration factor = 373	-	Courtney & Langston, 1978
Rotifer, *Brachionus plicatilis*	Aroclor® 1254	45 days	Bioconcentration factor = 340,000 in lipid and 51,000 in dry tissue	-	Scura & Theilacker, 1977
Eastern oyster, *Crassostrea virginica*	Aroclor® 1254	2 days	Bioconcentration factor = 8,100	-	Duke, et al. 1970
Eastern oyster, *Crassostrea virginica*	Aroclor® 1254	24 wks	Reduced growth	5.0	Lowe, et al. 1972

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Horseshoe crab, *Limulus polyphemas*	Aroclor® 1016	96 days	Bioconcentration factor = 1,298	-	Neff & Giam, 1977
Amphipod, *Gammarus oceanicus*	Aroclor® 1254	30 days	Mortality	≥10	Wildish, 1970
Grass shrimp, *Palaemonetes pugio*	Aroclor® 1254	1 hr	Avoidance	10	Hansen, et al. 1974b
Grass shrimp, *Palaemonetes pugio*	Aroclor® 1254	4 days	Water efflux affected and altered metabolic state	25-45	Roesijadi, et al. 1976a,b
Pink shrimp, *Penaeus duorarum*	Aroclor® 1248	48 hrs	LC50	32	Lowe, undated
Pink shrimp, *Penaeus duorarum*	Aroclor® 1254	48 hrs	LC50	32	Lowe, undated
Pink shrimp, *Penaeus duorarum*	Aroclor® 1254	15 days	51% mortality	0.94	Nimmo, et al. 1971
Pink shrimp, *Penaeus duorarum*	Aroclor® 1254	15 days	LC50	1.0	Nimmo & Bahner, 1976
Pink shrimp, *Penaeus duorarum*	Aroclor® 1254	2 days	Bioconcentration factor = 140	-	Duke, et al. 1970
Fiddler crab, *Uca pugilator*	Aroclor® 1242	4 days	Greater dispersion of melanin	2,000	Fingerman & Fingerman, 1978
Fiddler crab, *Uca pugilator*	Aroclor® 1254	38 days	Inhibited molting	8.0	Fingerman & Fingerman, 1977
Communities of organisms	Aroclor® 1254	4 mos	Affected composition	0.6	Hansen, 1974
Northern anchovy, *Engraulis mordax*	Aroclor® 1254	45 days	Bioconcentration factor = 13,000,000 in lipid and 1,030,000 in dry tissue	-	Scura & Theilacker, 1977

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)	Reference
Spot, *Leiostomus xanthurus*	Aroclor® 1254	-	Liver pathogenesis	5.0	Nimmo, et al. 1975
Spot, *Leiostomus xanthurus*	Aroclor® 1254	20-45 days	51 to 62% mortality	5.0	Hansen, et al. 1971
Pinfish, *Lagodon rhomboides*	Aroclor® 1254	1 hr	Avoidance	10.0	Hansen, et al. 1974b
Pinfish, *Lagodon rhomboides*	Aroclor® 1254	14-35 days	41 to 66% mortality	5.0	Hansen, et al. 1971
Pinfish, *Lagodon rhomboides*	Aroclor® 1254	2 days	Bioconcentration factor = 980	-	Duke, et al. 1970
Pinfish, *Lagodon rhomboides*	Aroclor® 1016	42 days	50% mortality	21.0	Hansen, et al. 1974a
Sheepshead minnow (adult), *Cyprinodon variegatus*	Aroclor® 1254	28 days	Lethargy, reduced feeding, fin rot, mortality	10	Hansen, et al. 1973
Sheepshead minnow (juvenile), *Cyprinodon variegatus*	Aroclor® 1254	21 days	Mortality	10	Schimmel, et al. 1974
Sheepshead minnow (embryos and fry), *Cyprinodon variegatus*	Aroclor® 1254	21 days	LC50	0.93	Schimmel, et al. 1974
Sheepshead minnow, *Cyprinodon variegatus*	Aroclor® 1254	28 days	Affected reproduction*	0.14	Hansen, et al. 1973

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*Significantly affected hatching of embryos or the survival of fry from exposed adults.

REFERENCES

Addison, R.F., et al. 1978. Induction of hepatic mixed-function oxidase (MFO) enzymes in trout (Salvelinus fontinalis) by feeding Aroclor® 1254 or 3-methylcholanthrene. Comp. Biochem. Physiol. 61C: 323.

Aulerich, R.J. and R.K. Ringer. 1977. Current status of PCB toxicity to mink, and effect on their reproduction. Arch. Environ. Contam. Toxicol. 6: 279.

Aulerich, R.J., et al. 1973. Reproductive failure and mortality in mink fed on Great Lakes fish. Jour. Repro. Fert. Suppl. 19: 365.

Bills, T.D. and L.L. Marking. 1977. Effects of residues of the polychlorinated biphenyl Aroclor® 1254 on the sensitivity of rainbow trout to selected environmental contaminants. Prog. Fish-Cult. 39: 150.

Birge, W.J., et al. 1979. Toxicity of organic chemicals to embryo-larval stages of fish. Ecol. Res. Ser. EPA 560/11-79-007. U.S. Environ. Prot. Agency, Washington, D.C.

Branson, D.R., et al. 1975. Bioconcentration of 2, 2', 4, 4'-tetrachlorobiphenyl in rainbow trout as measured by an accelerated test. Trans. Am. Fish. Soc. 104: 785.

Bryan, A.M. and P.G. Olafsson. 1978. The effect of polychlorobiphenyls (Aroclor® 1242) on bicarbonate-14 uptake by *Euglena gracilis*. Bull. Environ. Contam. Toxicol. 19: 374.

Butler, P.A. and R.L. Schultzman. 1978. Residues of pesticides and PCBs in estuarine fish, 1972-1976. Nat. Pestic. Monit. Prog. Pestic. Monit. Jour. 12: 51.

Camp, B.J., et al. 1974. Acute effects of Aroclor® 1254 (PCB) on *Ictalurus punctatus* (catfish). Bull. Environ. Contam. Toxicol. 12: 204.

Cooley, N.R., et al. 1972. Mirex and Aroclor® 1254: Effect on and accumulation by *Tetrahymena pyriformis* Strain W. Jour. Protozool. 19: 636.

Cooley, N.R., et al. 1973. The polychlorinated biphenyls, Aroclor® 1248 and 1260: Effect on and accumulation by *Tetrahymena pyriformis*. Jour. Protozool. 20: 443.

Couch, J.A. and D.R. Nimmo. 1974a. Ultrastructural studies by shrimp exposed to the pollutant chemical, polychlorinated biphenyl (Aroclor® 1254). Bull. Soc. Pharmacol. Environ. Pathol. 11: 17.

Couch, J.A. and D.R. Nimmo. 1974b. Detection of Interaction Between Natural Pathogens and Pollutant Chemicals in Aquatic Animals. *In*: Proceedings of Gulf Coast Regional Symposium on Diseases of Aquatic Animals. LSU-SG-74-05. p. 261.

Courtney, W.A. and W.J. Langston. 1978. Uptake of polychlorinated biphenyl (Aroclor® 1254) from sediment and from seawater in two intertidal polychaetes. Environ. Pollut. 15: 303.

Cutkomp, L.K., et al. 1972. The sensitivity of fish ATPase to polychlorinated biphenyls. Environ. Health Perspect. April: 165.

Davis, P.W., et al. 1972. Organochlorine insecticide, herbicide and polychlorinated biphenyl (PCB) inhibition of Nak-ATPase in rainbow trout. Bull. Environ. Contam. Toxicol. 8: 69.

DeFoe, D.L., et al. 1978. Effects of Aroclor® 1248 and 1260 on the fathead minnow (*Pimephalis promelas*). Jour. Fish. Res. Board Can. 35: 997.

Desaiah, D., et al. 1972. Inhibition of oligomycin-sensitive and insensitive magnesium adenosine triphosphatase activity in fish by polychlorinated biphenyls. Biochem. Pharmacol. 21: 857.

Duke, T.W., et al. 1970. A polychlorinated biphenyl (Aroclor® 1254) in the water, sediment and biota of Escambia Bay, Florida. Bull. Environ. Contam. Toxicol. 5: 171.

Ewald, W.G., et al. 1976. Toxicity of polychlorinated biphenyls (PCBs) to *Euglena gracilis*: Cell population, growth, carbon fixation, chlorophyll level, oxygen consumption, and protein and nucleic acid synthesis. Bull. Environ. Contam. Toxicol. 16: 71.

Fingerman, S.W. and M. Fingerman. 1977. Effects of a polychlorinated dibenzofuran on molting of the fiddler crab, Uca pugilator. Bull. Environ. Contam. Toxicol. 18: 138.

Fingerman, S.W. and M. Fingerman. 1978. Influences of the polychlorinated biphenyl preparation Aroclor® 1254 on color changes of the fiddler crab Uca pugilator. Mar. Biol. 50: 37.

Fisher, K.S., et al. 1974. Effects of PCB on interspecific competition in natural and anotobiotic phytoplankton communities in continuous and batch cultures. Microbiol. Ecology. 1: 39.

Fisher, N.S. 1975. Chlorinated hydrocarbon pollutants and photosynthesis of marine phytoplankton: A reassessment. Science. 189: 463.

Fisher, N.S. and C.F. Wurster. 1973. Individual and combined effects of temperature and polychlorinated biphenyls on the growth of three species of phytoplankton. Environ. Pollut. 5: 105.

Fowler, S.U., et al. 1978. Polychlorinated biphenyls: Accumulation from contaminated sediments and water by the polychaete Nereis diversicolor. Mar. Biol. 48: 303.

Frederick, L.L. 1975. Comparative uptake of a polychlorinated biphenyl and dieldrin by the white sucker (Catostomus commersoni). Jour. Fish. Res. Board Can. 32: 1705.

Freeman, H.C. and D.R. Idler. 1975. The effect of polychlorinated biphenyl on steroidogenesis and reproduction in the brook trout (Salvelinus fontinalis). Can. Jour. Biochem. 53: 666.

Gruger, E.H., et al. 1976. Sublethal effects of structurally related tetrachloro-, pentachloro-, and hexachlorobiphenyl on juvenile coho salmon. Environ. Sci. Technol. 10: 1033.

Gruger, E.H., et al. 1977. Induction of hepatic aryl hydrocarbon hydroxylase in salmon exposed to petroleum dissolved in seawater and to petroleum and polychlorinated biphenyls, separate and together in food. Bull. Environ. Contam. Toxicol. 17: 512.

Haile, C.L., et al. 1975. Chlorinated hydrocarbons in the Lake Ontario ecosystem (IFYGL). Ecol. Res. Ser. EPA 660/3-75-022. U.S. Environ. Prot. Agency, Corvallis, Oregon.

Halter, M.T. 1974. The acute toxicity of polychlorinated biphenyl, Aroclor® 1254, to the early life stages of coho salmon and steelhead trout. PCB Newslett. Aug. 5. Natl. Water. Qual. Lab., Duluth, Minnesota.

Halter, M.T. and H.E. Johnson. 1974. The acute toxicities of polychlorinated biphenyl (PCB) and DDT alone and in combination to early life stages of coho salmon (Oncorhynchus kisutch). Jour. Fish. Res. Board Can. 31: 1543.

Hansen, D.J. 1974. Aroclor® 1254: Effect of composition of developing estuarine animal communities in the laboratory. Contrib. Mar. Sci. 18: 19.

Hansen, D.J. 1975. PCBs: Effects on and accumulation by estuarine organisms. National Conference on Polychlorinated Biphenyls. EPA 560/6-75-004. p. 282.

Hansen, D.J. 1980. Memorandum to C.E. Stephan. July.

Hansen, D.J., et al. 1971. Chronic toxicity, uptake and retention of Aroclor® 1254 in two estuarine fishes. Bull. Environ. Contam. Toxicol. 6: 113.

Hansen, D.J., et al. 1973. Aroclor® 1254 in eggs of sheepshead minnows: Effect on fertilization success and survival of embryos and fry. Proc. 27th Annu. Conf. S.E. Assoc. Game Fish Comm. p. 420.

Hansen D.J., et al. 1974a. Aroclor® 1016: Toxicity to and uptake by estuarine animals. Environ. Res. 7: 363.

Hansen, D.J., et al. 1974b. Avoidance of Aroclor® 1254 by shrimp and fishes. Bull. Environ. Contam. Toxicol. 12: 253.

Hansen, D.J., et al. 1975. Effects of Aroclor® 1016 on embryos, fry, juveniles, and adults of sheepshead minnows (*Cyprinodon variegatus*). Trans. Am. Fish. Soc. 104: 584.

Hansen, L.G., et al. 1976. Effects of dietary Aroclor® 1242 on channel catfish (*Ictalurus punctatus*) and the selective accumulation of PCB components. Jour. Fish. Res. Board Can. 33: 1343.

Harding, L.W., Jr. and J.H. Phillips, Jr. 1978. Polychlorinated biphenyl (PCB) effects on marine phytoplankton photosynthesis and cell division. Mar. Biol. 49: 93.

Hawes, M.L., et al. 1976a. The effects of various Aroclor® fractions on the population growth of *Chlorella pyrenoidosa*. Bull. Environ. Contam. Toxicol. 15: 14.

Hawes, M.L., et al. 1976b. The effects of various Aroclor® fractions on the productivity of *Chlorella pyrenoidosa*. Bull. Environ. Contam. Toxicol. 15: 588.

Hermanutz, R. and F. Puglisi. 1976. Comparative toxicity of Aroclor® 1016 and 1242 to flagfish (*Jordanella floridae*) and fathead minnow (*Pimephales promelas*). Duluth, Minnesota. (Manuscript)

Hesse, J.L. 1973. Status report on polychlorinated biphenyls in Michigan waters. Mich. Water Res. Comm. June, 1973.

Hogan, J.W. and J.E. Brauhn. 1975. Abnormal rainbow trout fry from eggs containing high residues of a PCB (Aroclor® 1242). Prog. Fish. Cult. 37: 229.

Ito, Y. 1973. Studies on the influence of PCB on aquatic organisms-II. Changes in blood characteristics and plasma enzyme activities of carp administered orally with PCB. Bull. Jap. Soc. Sci. Fish. 39: 1135.

Ito, Y. and T. Murata. 1974. Studies on the influence of PCB on aquatic organisms-IV. Changes in serum lipid contents and formation of lipid peroxide in the tissues of carp administered with PCB orally. Bull. Jap. Soc. Sci. Fish. 40: 261.

Johansson, N., et al. 1972. Metabolic effects of PCB (polychlorinated biphenyls) on the brown trout (Salmo trutta). Comp. Gen. Pharmacol. 3: 310.

Keil, J.E., et al. 1971. Polychlorinated biphenyl (Aroclor® 1242): Effects of uptake on growth, nucleic acids, and chlorophyll of a marine diatom. Bull. Environ. Contam. Toxicol. 6: 156.

Koch, R.B., et al. 1972. Polychlorinated bipohenyls: Effect of long-term exposure on ATPase activity in fish, Pimephales promelas. Bull. Environ. Contam. Toxicol. 7: 87.

Laird, E.J. 1973. Sensitivity of Dunaliella and Scenedesmus (Chlorophyceae) to chlorinated hydrocarbons. Phycologia. 12: 29.

Larsson, C.M. and J.E. Tillberg. 1975. Effects of the commercial polychlorinated biphenyl mixture Aroclor® 1242 on growth, viability, phosphate uptake, respiration and oxygen evolution, in Scenedesmus. Physiol. Plant. 33: 256.

Lidman, U., et al. 1976. Induction of the drug metabolizing system in rainbow trout (Salmo gairdneri) liver by polychlorinated biphenyls (PCBs). Acta Pharmacol. Toxicol. 39: 262.

Lowe, J.I. Results of toxicity tests with fishes and macroinvertebrates. Data sheets available from Environ. Res. Lab. U.S. Environ. Prot. Agency, Gulf Breeze, Florida.

Lowe, J.I., et al. 1972. Effects of the polychlorinated biphenyl Aroclor® 1254 on the American oyster, Crassostrea virginica. Mar. Biol. 17: 209.

Maki, A.W. and H.E. Johnson. 1975. Effects of PCB (Aroclor® 1254) and p, p'-DDT on production and survival of Daphnia magna Strauss. Bull. Environ. Contam. Toxicol. 13: 412.

Martell, J.M., et al. 1975. PCBs in suburban watershed, Reston, Va. Environ. Sci. Technol. 9: 872.

Mauck, W.L, et al. 1978. Effects of the polychlorinated biphenyl Aroclor® 1254 on growth, survival, and bone development in brook trout (Salvelinus fontinalis). Jour. Fish. Res. Board Can. 35: 1084.

Mayer, F.L., et al. 1977. Residues dynamics and biological effects of polychlorinated biphenyls in aquatic organisms. Arch. Environ. Contam. Toxicol. 5: 501.

Moore, S.A. and R.C. Harriss. 1972. Effects of polychlorinated biphenyl on marine phytoplankton communities. Nature. 240: 356.

Morgan, J.R. 1972. Effects of Aroclor® 1242 (a polychlorinated biphenyl) and DDT on cultures of an alga, protozoan, daphnid, ostracod, and guppy. Bull. Environ. Contam. Toxicol. 8: 129.

Mosser, J.L., et al. 1972a. Polychlorinated biphenyls: Toxicity to certain phytoplankters. Science. 174: 191.

Mosser, J.L., et al. 1972b. Polychlorinated biphenyls and DDT alter species composition in mixed cultures of algae. Science. 175: 533.

Nadeau, R.J. and R.A. Davis. 1976. Polychlorinated biphenyls in the Hudson River (Hudson Falls - Fort Howard, New York State). Bull. Environ. Contam. Toxicol. 16: 436.

Nebeker, A.V. and F.A. Puglisi. 1974. Effect of polychlorinated biphenyls (PCBs) on survival and reproduction of *Daphnia*, *Gammarus*, and *Tanytarsus*. Trans. Am. Fish. Soc. 103: 722.

Nebeker, A.V., et al. 1974. Effect of polychlorinated biphenyl compounds on survival and reproduction of the fathead minnow and flagfish. Trans. Am. Fish. Soc. 103: 562.

Neff, J.M. and C.S. Giam. 1977. Effects of Aroclor® 1016 and Halowax® 1099 on Juvenile Horseshoe Crabs *Limulus polyphemus*. *In*: Physiological Responses of Marine Biota to Pollutants. Academic Press, New York. p. 21.

Nestel, H. and J. Budd. 1974. Chronic oral exposure of rainbow trout (*Salmo gairdneri*) to a polychlorinated biphenyl (Aroclor® 1254): Pathological effects. Can. Jour. Comp. Med. 39: 208.

Nimmo, D.R. and L.H. Bahner. 1974. Some Physiological Consequences of Polychlorinated Biphenyl- and Salinity-Stress in Penaeid Shrimp. *In*: Pollution and Physiology at Marine Animals. Academic Press, Inc., New York. p. 427.

Nimmo, D.R. and L.H. Bahner. 1976. Metals, Pesticides and PCB: Toxicities to Shrimp Singly and in Combination. *In*: Estuarine Processes. Vol. I. Uses, Stresses, and Adaptation to the Estuary. Academic Press, Inc., New York.

Nimmo, D.R., et al. 1971. Toxicity and distribution of Aroclor® 1254 in the pink shrimp, *Penaeus duorarum*. Mar. Biol. 11: 191.

Nimmo, D.R., et al. 1974. Accumulation of Aroclor® 1254 in grass shrimp (*Palaemonetes pugio*) in the laboratory and field exposures. Bull. Environ. Contam. Toxicol. 11: 303.

Nimmo, D.R., et al. 1975. Toxicity of Aroclor® 1254 and its physiological activity in several estuarine organisms. Arch. Environ. Contam. Toxicol. 3: 22.

Norstrom, R.J., et al. 1976. A bioenergentics-based model for pollutant accumulation by fish. Simulation of PCB and methyl-mercury residue levels in Ottawa river yellow perch (Perca flavescens). Jour. Fish. Res. Board Can. 33: 248.

O'Conners, H.B., Jr., et al. 1978. Polychlorinated biphenyls may alter marine trophic pathways by reducing phytoplankton size and production. Science. 201: 737.

Parejko, R., et al. 1975. Chlorhydrocarbons in Lake Superior lake trout (Salvelinus namaycush). Bull. Environ. Contam. Toxicol. 14: 480.

Parrish, P.R., et al. 1974. Effects of polychlorinated biphenyl, Aroclor® 1016, on estuarine animals. Assoc. S.E. Biol. Bull. 21: 74.

Platonow, N.S. and L.H. Karstad. 1973. Dietary effects of polychlorinated biphenyls on mink. Can. Jour. Comp. Med. 37: 391.

Ringer, R.K., et al. 1972. Effect of dietary polychlorinated biphenyls on growth and reproduction of mink. Am. Chem. Soc. Natl. Meet. Preprint Pap. 12: 149.

Roesijadi, G., et al. 1976a. Osmoregulation of grass shrimp Palaemonetes pugio exposed to polychlorinated biphenyls (PCBs). I. Effect on chloride and osmotic concentrations and chloride and water-exchange kinetics. Mar. Biol. 38: 343.

Roesijadi, G., et al. 1976b. Osmoregulation of the grass shrimp *Paslaemonetes pugio* exposed to polychlorinated biphenyls (PCBs). II. Effect on free amino acids of muscle tissue. Mar. Biol. 38: 357.

Sanborn, J.R. 1974. The fate of select pesticides in the aquatic environment. Ecol. Res. Ser. EPA 660/3-74-025. U.S. Environ. Prot. Agency, Corvallis, Oregon.

Sanders, H.O. and J.H. Chandler. 1972. Biological magnification of a polychlorinated biphenyl (Aroclor®) from water by aquatic invertebrates. Bull. Environ. Contam. Toxicol. 7: 257.

Schimmel, S.C., et al. 1974. Effects of Aroclor® 1254 on laboratory-reared embryos and fry of sheepshead minnows (*Cyprinodon variegatus*). Trans. Am. Fish. Soc. 103: 582.

Schoor, W.P. 1975. Problems associated with low-solubility compounds in aquatic toxicity tests: Theoretical model and solubility characteristics of Aroclor® 1254 in water. Water Res. 9: 937.

Scura, E.O. and J.H. Theilacker. 1977. Transfer of the chlorinated hydrocarbon PCB in a laboratory marine food chain. Mar. Biol. 40: 317.

Snarski, V.M. and F.A. Puglisi. 1976. Effects of Aroclor® 1254 on brook trout, *Salvelinus fontinalis*. Ecol. Res. Ser. EPA 600/3-76-112. U.S. Environ. Prot. Agency, Duluth, Minnesota.

Stalling, D.L. 1971. PCB residues in bluegills and channel catfish exposed to Aroclor® 1248 and Aroclor® 1254 for 11 weeks. PCB Newletter. July 28. Duluth, Minnesota.

Tejedor, M.C. et al. 1979. Oxidative metabolism in Saccharomyces cerevissiae as affected by polychlorinated biphenyls. Bull. Environ. Contam. Toxicol. 22: 439.

Veith, G. 1975. Baseline concentrations of polychlorinated biphenyls and DDT in Lake Michigan fish, 1971. Pestic. Monitor. Jour. 9: 21.

Veith, G. 1976. Comparative toxicity of A-1016 and A-1242 to the fathead minnow. Environ. Res. Lab. U.S. Environ. Prot. Agency, Duluth, Minnesota. (Manuscript)

Veith, G.D., et al. 1977. Residues of PCBs and DDT in the western Lake Superior ecosystem. Arch. Environ. Contam. Toxicol. 5: 487.

Weininger, D. 1978. Accumulation of PCBs by lake trout in Lake Michigan. Ph.D. Thesis, Univ. of Wisconsin.

Wiese, C.S. and D.A. Griffin. 1978. The solubility of Aroclor® 1254 in seawater. Bull. Environ. Contam. Toxicol. 20: 403.

Wildish, D.J. 1970. The toxicity of polychlorinated biphenyls (PCB) in seawater to Gammarus oceanicus. Bull. Environ. Contam. Toxicol. 5: 202.

Yap, H.H., et al., 1971. Sensitivity of fish ATPases to polychlorinated biphenyls. Nature. 233: 61.

Zitko, V. 1970. Polychlorinated biphenyls (PCB) solubilized in water by nonionic surfactants for studies of toxicity to aquatic animals. Bull. Environ. Contam. Toxicol. 5: 279.

Zitko, V. and W.G. Carson. 1977. A comparison of the uptake of PCB and Isopropyl-PCBs (chloralkylene 12) by fish. Chemosphere. No. 2/3. Pergammon Press.

Zullei, H. and G. Benecke. 1978. Application of a new bioassay to screen the toxicity of polychlorinated biphenyls in blue-green algae. Bull. Environ. Contam. Toxicol. 20: 786.

Mammalian Toxicology and Human Health Effects

SUMMARY

Polychlorinated biphenyls (PCBs) have been used commercially since 1929 as dielectric and heat exchange fluids and in a variety of other applications. They have become widely disseminated in the environment worldwide. Like many organochlorine pesticides, they are highly persistent and accumulate in food webs. Human exposure to PCBs has resulted largely from the consumption of contaminated food but also from inhalation and skin absorption in work environments. PCBs accumulate in the fatty tissues and skin of man and other mammals. Metabolism occurs by hydroxylation and dihydrodiol formation with arene oxides as probable intermediates. The rate of metabolism and excretion slows dramatically as the chlorination of the biphenyl nucleus increases. Arrangement of chlorines which eliminate adjacent unsubstituted carbons greatly increase resistance to metabolism. PCBs have caused profound toxic effects in man and animals, particularly if repeated exposures occur. The skin and liver are major sites of pathology, with the gastrointestinal tract and nervous systems also being targets. Polychlorodibenzofurans which contaminate commercial PCB mixtures may contribute significantly to their toxicity. Several studies in rodents suggest strongly that some PCBs are carcinogenic and that they can enhance the carcinogenicity of other chemicals. A linear model for risk assessment has been used to estimate maximum safe levels in water and fish which will establish a level of risk for the human population from cancer. A maximum level of PCBs in water projected to result in no more than one cancer in 10^5 individuals with lifetime exposure of 0.79 ng/l is suggested by the analysis.

EXPOSURE

The magnitude of the dispersal of these chemicals is revealed by their detection in the tissues of plants and animals in all parts of the world. PCB residues have been observed in wildlife in Sweden, North America, Great Britain, the Netherlands, and even the Arctic (Risebrough and deLappe, 1972). Because PCBs are not naturally occurring substances, their dissemination is entirely the result of human activity. Their entry into the environment has occurred by vaporization into the atmosphere, and by spilling or dumping into water or onto land. It has been estimated that of the 1970 sales of PCBs in North America, only 20 percent represented a net increase in the total amount in service. Estimated sources of loss for that year were 1 - 2 x 10^3 tons for evaporation; 4 - 5 x 10^3 tons for leaks and disposal of fluids; and 22 x 10^3 tons for disposal by incineration and burial (Nisbet and Sarofim, 1972). The cumulative input to the environment between 1930 and 1970 was estimated to be 3 x 10^4 tons to air, 6 x 10^4 tons to fresh and coastal waters, and 3 x 10^5 tons to dumps and landfills. In that time, up to one-third of the PCBs released to air and one-half of that released to water were probably degraded. Degradation in landfills is more difficult to estimate (Nisbet and Sarofim, 1972). PCBs have been found repeatedly to be widespread in analyses of human tissues. For example, detectable levels of PCBs have been reported in adipose tissue samples of up to 91 percent of individuals sampled in a survey of the United States population (Kutz and

Strassman, 1976; see Table 13). This finding suggests that environmental contamination may be a significant source of human exposure. Likely routes of exposure for the general population are water and particularly food, while inhalation and dermal contact are likely to be more significant routes in occupational exposure.

Ingestion from Water

The solubility of PCBs in water is very low, decreasing as the percent chlorination is raised. Solubilities of Aroclors in water at 20°C vary from 200 μg/1 for 1242 to about 25 μg/1 for 1260 (Nisbet and Sarofim, 1972). The major factors in the dynamics of PCB distribution in water are its low solubility, high specific gravity, and its high affinity for solids. Most PCBs discharged into water are found in bottom sediments near the site of discharge (Nisbet and Sarofim, 1972). Evaluation of PCB levels in surface waters and bottom sediments of the major drainage basins of the United States was conducted between 1971 and 1974 (Dennis, 1976). The data were derived from the U.S. Geological Survey (USGS) study of 1971-72 (Crump-Weisner, et al. 1974) and from additional data collected by the USGS between 1972 and 1975 (PCB data base 1972-75). It is summarized in detail in the Criteria Document for PCBs (U.S. EPA, 1976a). The highest concentrations in both water and sediment were found in the basins east of the Mississippi River. The highest levels were found in 1971 in the lower Mississippi basin, with a median concentration for the region of 3.0 μg/1 and positive detections at 100 percent of stations tested. Over the time period of the study the concentrations and incidences of PCBs detected in all basins have decreased substantially. By 1974 the median level in the lower Mississippi basin had dropped to 0.1 μg/l and the incidence of detection to 2.6 percent of stations tested. The levels in sediments, however, have persisted at much higher levels over this period of time. In 1971 median sediment levels for the Mississippi basin were 30 μg/kg and the incidence of detection 100 percent. By 1974 the incidence had dropped to 9.9 percent, and the median level was 10.5 μg/kg.

Although PCBs are widespread in aquatic environments (Peakall, 1975), their low solubility generally prevents them from reaching high concentrations in drinking water supplies. The persistence of PCBs and their accumulation in sediments, however, increase the significance of water as a source of human exposure by providing a reservoir of material which can continue to contaminate water long after the addition of PCBs has ceased. In combination with these factors, the lipophilicity of PCBs results in their continued introduction to, and accumulation in, the food chain. As a consequence, fish and other foods obtained from aquatic environments may become important sources of exposure even if PCB levels in the water are low.

The ability of PCBs discharged from a manufacturing facility to contaminate a drinking water system has recently been highlighted. Billings, et al. (1978) determined the levels of PCBs in the Easley-Central Water District, Pickens County, South Carolina. They observed that PCBs discharged by a capacitor manufacturing facility 12 km upstream from the water district's treatment plant were entering the water system. Finished potable water supplies were contaminated to levels as high as 818 ng/l.

Ingestion from Food

Contamination of food with PCBs occurs primarily by three mechanisms. The first is contamination of human food as a consequence of accumulation in the food chain. The contamination of freshwater fish as a consequence of the contamination of the aquatic environment is a particularly significant route of PCB entry into the human diet which will be discussed in more detail below. The second mechanism occurs by the direct contamination of feeds or foodstuffs with PCBs. This may occur as a result of accidental spills or equipment malfunctions as was the case in the episode of rice oil contamination in Japan which led to the outbreak of Yusho or rice oil disease in 1968 (Kuratsune, et al. 1976). In this instance leaks in a heat exchanger used to process rice bran oil resulted in the contamination of the oil by the exchanger fluid (Kanechlor 400). Discovery of the contamination was made only after numerous cases of chlorinated hydrocarbon intoxication in Fukuoka prefecture, Japan. The oil was found to contain 2,000 to 3,000 ppm Kanechlor 400 which was contaminated with polychlorodibenzofurans (1.6 to 5 ppm). Average consumption of PCBs among affected individuals was estimated to be 2 g (Kuratsune, et al. 1972). By 1975 the total number of known individuals affected was 1,291. Elevated PCB levels in fat were still observed four years after the exposure, and dermatological symptoms were found in up to 89 percent of a group of 72 patients examined in 1973 or 1974. An example of accidental PCBs contamination in animal feed occurred as a result of the use of PCBs in silo coatings (Willett and Hess, 1975). The third significant source of PCBs in foodstuffs was food packaging made from recycled paper containing PCBs (Jelinek and Corneliussen, 1976).

A special case of human exposure via food which must be considered is human breast milk. Adverse effects have been observed in breast fed infants of women with Yusho (Kuratsune, et al. 1976) and in infant Rhesus monkeys ingesting breast milk containing 7 to 16 ppm PCBs (fat basis) (Allen, 1975; Allen and Barsotti, 1976). Preliminary survey data indicate average PCB levels in human breast milk of 1.8 ppm (fat basis) (42 FR 17487), and a study of PCB exposed nursing mothers in Germany indicated average PCB levels of 3.5 ppm (Tombergs, 1972). The proximity of these values to the toxic levels in infant monkeys (7 to 16 ppm) suggests that human breast milk must be considered a significant source of PCB exposure.

The extent of contamination of the U.S. food supply has been the subject of Food and Drug Administration (FDA) and Department of Agriculture (USDA) monitoring programs since 1969. Results of these studies have been summarized by Jelinek and Corneliussen (1976). The initial analysis of 15,000 food samples between 1969 and 1971 is summarized in Table 1. The results of monitoring programs in fiscal years 1973, 1974, and 1975 are summarized in Table 2. Over the monitored period the incidence and levels of PCBs have dropped in all food classes. By 1975 the only significant food sources were fish, meat, and dairy products. Fish were by far the most significant source. The findings for the 1969-71 period led to the establishment of regulations for PCB levels in food (38 FR 18096). The temporary tolerances established at that

TABLE 1

Summary of PCBs in Food*
Nov., 1969 - June, 1971[a]

Food Commodity	Positive Findings[c]	Avg. of Positives (ppm)	Max. Level (ppm)
Finfish	317	2.1	35.3
Oysters	12	Trace	Trace
Fish by-products	6	1.8	5.0
Cheese	44	0.3[b]	1.0[b]
Milk	60	2.5[b]	22.8[b]
Eggs	17	Trace	0.5
Potato by-products	12	1.1	4.2
Miscellaneous	11	1.9	6.5

[a] Approximately 15,000 samples examined

[b] Fat basis

[c] Detection limits: fish 0.5 ppm, other foods 0.05 ppm (P.E. Corneliussen, personal communication)

*Source: Jelinek and Corneliussen, 1976

TABLE 2

Summary of PCBs in Foods*

Fiscal Years 1973, 1974, and 1975

Food Commodity	FY 1973		FY 1974		FY 1975	
	Percent Positive[b]	Max. (ppm)[a]	Percent Positive	Max. (ppm)[a]	Percent Positive	Max. (ppm)[a]
Fish	60.4	123.0	44.0	16.8	17.8	9.0
Milk	2.2	1.6	2.6	2.3	0.7	1.9
Eggs	1.1	Trace	4.2	11.0	0.0	N.D.
Cheese	0.9	0.5	2.6	2.8	0.0	N.D.
Feed components	12.7	9.0	0.0	N.D.	0.3	0.9
Animal feeds	7.2	199.5	0.0	N.D.	0.0	N.D.
Processed fruits	4.5	19.2	0.0	N.D.	0.0	N.D.
Infant and junior foods	1.1	Trace	0.0	N.D.	0.0	N.D.
	Percent Positive	Percent above 5 ppm[a]	Percent Positive	Percent above 5 ppm[a]	Percent Positive	Percent above 5 ppm[a]
Meats and poultry (USDA)	1.9	0.19	1.2	0.07	0.3	0.06

[a] Milk, cheese, meats and poultry reported as ppm, fat basis

[b] Detection limits: fish 0.5 ppm, other foods 0.05 ppm (P.E. Corneliussen, personal communication)

*Source: Jelinek and Corneliussen, 1976

time and new tolerances recommended in 1977 (42 FR 17487) are given in Table 3. The enforcement of those tolerances and restriction of PCB use in open systems after 1970 probably account for the general decline of PCB levels in foodstuffs.

Comprehensive fish surveys conducted by the FDA in fiscal years 1973 and 1974 indicated a drop in the incidence of PCB detection in fish from less than 30 percent in 1973 to less than 20 percent in 1974. In 1973, 3 percent contained over 1 ppm and 0.5 percent contained over 5 ppm PCBs. The data from all FDA studies in the fiscal years 1973, 1974, and 1975 are summarized in Figure 1. While the incidence of PCBs in fish dropped over the period, the fraction of positive fish containing over 5 ppm PCBs increased from less than 5 percent to over 10 percent. The samples containing more than 5 ppm were from the Great Lakes. Because the study involved different sources and objectives from year to year, no conclusion as to whether a significant trend existed was drawn. It should be noted that these surveys were conducted with fish in commerce and provide no information about sport fish per se. The studies indicated that significant levels of PCBs generally do not occur in saltwater fish.

The impact of sport fish consumption was examined in a study of a group of sports fishermen who consumed an average of 24 to 25 pounds of fish annually (highest individual exposure 180 lbs/year over a two-year period). PCB residues in cooked fish ranged from 0.35 - 5.38 ppm. Plasma PCB levels ranged from a high of 0.366 ppm in the exposed group to control levels of 0.007 ppm (less than six lbs consumed per year) (42 FR 17487).

TABLE 3

FDA Regulations for PCBs*

I. Temporary tolerances

Commodity	PCB conc. (ppm)	Proposed Guidelines 1977
Milk (fat basis)	2.5	1.5
Dairy products (fat basis)	2.5	1.5
Poultry (fat basis)	5.0	3.0
Eggs	0.5	0.3
Finished animal feed	0.2	0.2
Animal feed components	2.0	2.0
Fish (edible portion)	5.0	2.0
Infant and junior foods	0.2	pending
Paper food-packaging material without PCB-impermeable barrier	10.0[a]	

[a] Administrative guideline, pending hearing

*Source: Jelinek and Corneliussen, 1976
42 FR 17487

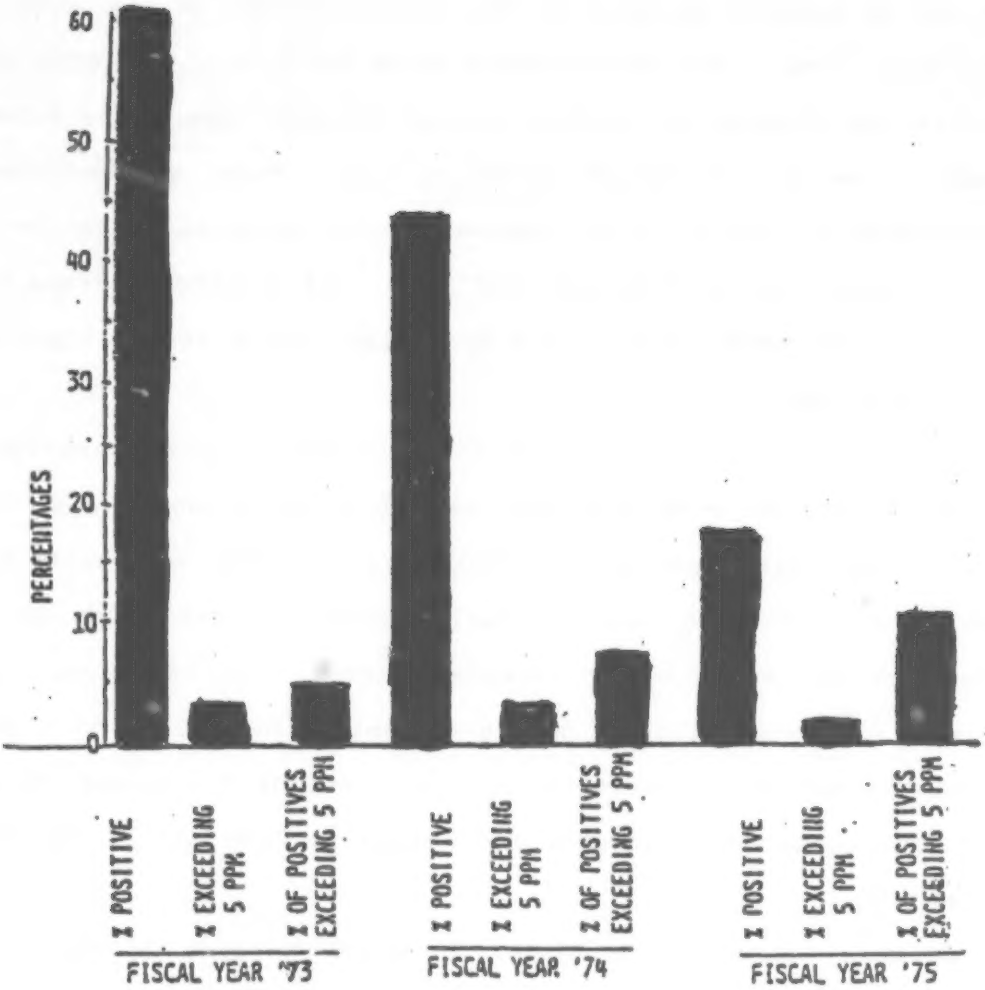


FIGURE 1

PCBs in Fish FY 73, 74, 75 (Level of detection: 0.5 ppm)

Source: Jelinek and Corneliusen, 1976

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

Several laboratory studies, in which percent lipids and a steady-state BCF were measured, have been conducted on polychlorinated biphenyls. The mean of the BCF values, after normalization to one percent lipids, is 10,385 (see Table 5 in Aquatic Life Toxicology section). An adjustment factor of 3 can be used to adjust the mean normalized BCF to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for polychlorinated biphenyls and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 31,200.

Higher BCF values apparently can be achieved in field exposures (Haile, et al. 1975; Norstrom, et al. 1976; Duke, et al. 1970; Nimmo, et al. 1975; Veith, 1975; Veith, et al. 1977), but those values cannot be considered quantitative because the exposure of the organism cannot be adequately documented and integrated over a long enough period of time.

In order to estimate human dietary PCB intake, the FDA conducts a continuing survey of the total diet. Composites of 12 different food categories are analyzed for PCB content. Table 4 summarizes the results of the survey from 1971 through the first half of 1975. While contamination was observed in most categories in 1972, the number of positive categories had dropped by 1973. In 1974 and 1975 only meat, fish, and poultry were observed to contain PCBs; fish was almost always the contributor of positive results in that category (Jelinek and Corneliussen, 1976). Most of the contamination noted in the other categories in earlier years was thought to result from exposure during processing or packaging because the raw foods were rarely found to contain PCBs. Total daily intake, calculated from the composite figures for a young adult male over the period 1971-75, is summarized in Table 5. Total daily intake dropped by almost 50 percent over the period, but intake in the meat-fish-poultry category changed very little. By 1974, almost all of the dietary intake resulted from the ingestion of PCB-contaminated fish. The measures taken in the early 1970's to limit the release of PCBs into the environment and to remove them from food processing environments effectively reduced direct contamination of foodstuffs to a minimum level. The persis-

TABLE 4

Percent of Composites Containing PCBs,
from the FDA Total Diet Studies*

Fiscal Year	Dairy Products	Meat, Fish & Poultry	Grain and Cereal Prods.	Potatoes	Legume Vegetables	Root Vegetables	Garden Fruits	Oils, fats & Shortening	Sugars and Adjuncts
1971		47	13						
1972	6	46	6		6	3	3	17	6
1973	10	33	17	3				3	
1974		43							3
1975 (1st half)		40							

*Source: Jelinek and Corneliussen, 1976

TABLE 5

Estimates of Daily PCB Intakes*
(Total Diet Study - Teenage Male)

Fiscal Year	Average Daily Intake of PCBs[a]	
	Total Diet (μg/day)	Meat-fish-poultry Food Class (μg/day)
1971	15.0	9.5
1972	12.6	9.1
1973	13.1	8.7
1974	8.8	8.8
1975 (1st half)	8.7	8.7

[a] Lower limit of quantitative reporting = 0.05 ppm with analytical method employed

*Source: Jelinek and Corneliussen, 1976

tence of PCBs in aquatic environments and in fish has maintained a residual dietary exposure level. Further reduction of PCB levels in the diet will require that entry of PCBs into waterways be more tightly controlled and that monitoring of fish and other foods for PCB contamination be continued (Jelinek and Corneliussen, 1976). The recently recommended reduction of allowable PCB levels in fish to 2.0 ppm may further reduce dietary intake (42 FR 17487).

Two special situations which must be avoided to prevent unnecessary PCB ingestion should be mentioned. First, accidental contamination of foodstuffs or feeds with PCBs must be avoided. Although PCB manufacture is now stopping and distribution will cease in the near future, many PCB-containing products remain in service. Failure to exercise care in the maintenance and disposal of these units could result in the contamination of food or water. The tragic results of the episode of rice oil contamination in Japan (Kuratsune, 1972) provides ample evidence of the need for care and continued surveillance of foods. Second, although occupational exposure to PCBs will decline over the next several years, the possibility of food contamination as a consequence of transfer from workers' tools or clothing must be considered as a possible route of dietary exposure.

Inhalation

PCBs can enter the atmosphere by vaporization and may be found in either gaseous form or adsorbed to airborne particulates. Prior to the restriction of PCB use, substantial losses to the atmosphere resulted from evaporation of plasticizers and from improper incineration. In 1972, terrestrial input from fallout was estimated to be 1,000 to 2,000 tons/year. Annual emission rates were estimated at 1,500 to 2,500 tons (Nisbet and Sarofim, 1972). In 1975, a study of PCB content in air in suburban areas in Florida and Colorado indicated that average atmospheric levels were approximately 100 ng/m^3 (Kutz and Yang, 1976). Rates of fallout along the southern California coast were estimated to average 1,800 kg/year over a 50,000 km^2 area (Young, et al. 1976). The distribution of PCBs in air is nonuniform, being more highly concentrated in urban areas. The aerial fallout survey in southern California indicated that sectors in the urban areas around Los Angeles had fallout rates of up to 180 kg/yr, while less industrialized sectors had rates as low as 30 kg/yr. A study of PCB levels in soil samples showed that they were rarely detectable in agricultural soils but were found in 63 percent of urban samples from 19 cities (Carey and Gowan, 1976). General human exposure to inhaled PCBs probably varies with the local conditions. In relation to the 9 µg/day intake estimated from the diet (Jelinek and Corneliussen, 1976), nonoccupational exposures by inhalation are probably small.

While inhalation of PCBs is not and most likely will not be a major route of general human exposure, it is a highly significant route of occupational exposure. Early in its commercial use an association was observed between occupational exposure to PCB vapors and chloracne (Jones and Alden, 1936; Schwartz, 1936). The benefits of controlling leaks from closed systems into work environments were noted by Meigs, et al. (1954).

A study of occupational exposure in Japan found PCB vapors at levels between 13 and 540 $\mu g/m^3$ and airborne particulates between 4 and 650 µg/m^3 in a survey of six industrial plants. An additional finding of 6,270 µg/m^3 PCB particulates was associated with a spill. Blood PCB levels of 99 exposed workers averaged 370 ppb as compared to levels in 32 controls of 20 ppb (Hasegawa, et al. 1972). Ouw, et al. (1976) observed Aroclor 1242 levels between 2.22 and 0.32 mg/m^3 in different areas of an electrical equipment manufacturing facility in Australia. Blood Aroclor levels were analyzed by gas chromatography, and fractions with several retention times standardized against Aroclor 1242 were detected in exposed workers. Workers in an impregnation room where inhalation was a major mode of exposure had higher levels of PCBs than did workers in another area where exposure was primarily dermal. A series of 30 control individuals was not found to have detectable PCB levels. The limit of detection in this study was not reported; however, Finklea, et al. (1972) reports American control population blood levels of 0.3 to 3 ppb.

It is difficult to differentiate between industrial exposure by inhalation and dermal absorption (see Dermal section). Animal studies do indicate that animals exposed to PCB aerosols show rapid increases in liver PCB levels. Exposure to Pydranl A 200 for 15 minutes resulted in the accumulation in the liver of 50 percent of the PCBs accumulated after two hours (Benthe, et al. 1972). The lung appears to be a good site of absorption, and certain occupational environments contain significant levels of airborne PCBs. The National Institute for Occupational Safety and Health has recently proposed an occupational exposure limit of 1.0 µg/m^3 on a time weighted average 10-hour day, 40-hour week basis (NIOSH, 1977). Assuming a tidal air volume of 10 m^3 in an eight-hour day and 100 percent absorption, the resulting dose at this exposure level would be 10 μg/day.

Dermal

Dermal exposure, like inhalation exposure, is a particularly significant route in the occupational setting. With the restriction of PCB uses to sealed systems, the use of PCBs in products to which the public might be exposed has declined markedly, reducing opportunities for general exposure. Past uses of PCBs in carbonless copy paper, printer's inks, and other products probably contributed to general PCB exposures. Documented exposures are largely occupational as exemplified by the results of Ouw, et al. (1976). The authors noted that one group of employees was largely exposed through skin contact and had significantly elevated blood PCB levels.

In a variety of animal studies dermal application of several PCB-containing materials has produced both local and systemic effects including liver degeneration and death (Miller, 1944; Paribok, 1954; Vos and Beems, 1971). In neonatal rats treated by skin application with PCBs, a 5- to 10-fold increase in aryl hydrocarbonhydroxylase activity occurred in liver, skin, lung, and kidney, indicating significant distribution to these tissues after exposure by this route (Bickers, 1976; Bickers, et al. 1975).

The relative contributions of various routes of exposure can be expected to vary widely. Occupational exposures are by far the most severe with inhalation and skin contact being the major routes of absorption. A noteworthy by-product of occupational PCB exposure is the elevated risk of exposure among other members of workers' families. An epidemiological study in Bloomington, Indiana revealed significantly elevated serum PCB levels among a group of 18 occupationally exposed workers (mean 71.7 ppb) and a slight elevation among 19 members of their families (near 33.6 ppb) as compared to background levels (5 to 20 ppb) (McCloskey, et al. 1978). The general public is widely exposed to PCBs but at much lower levels and primarily through the diet. Fish living in contaminated waters are by far the largest contributors to dietary PCBs (Jelinek and Corneliussen, 1976).

PHARMACOKINETICS

Absorption

The efficiency of PCB absorption in the gut of rats was shown to be between 92 to 98.9 percent (Albro and Fishbein, 1972). Neither the degree of chlorination (mono-hexachlorobiphenyl) nor the dose ingested (5 to 100 mg/kg) markedly affected the efficiency of the uptake. Matthews and Anderson (1975b) observed a reduced accumulation of PCBs in adipose tissues of rats exposed orally as compared to intravenous (i.v.) injection. The differences were more pronounced with biphenyls of low chlorine content and were thought to be related to route of absorption and metabolic rates, rather than to the overall efficiency of transport across the gut. Absorption via the gut was also very efficient in adult Rhesus monkeys, 90 percent of a single dose of 1.5 or 3.0 g/kg Aroclor 1248 being absorbed from the gastrointestinal tract (Allen, et al. 1974a).

Efficient absorption via inhalation has been demonstrated in rats by Benthe, et al. (1972).

In humans, absorption via the intestine has been best illustrated by the Yusho Japan incident in 1968. Among individuals ingesting less than 720 ml of contaminated rice bran oil (equivalent to 1.5 to 2.2 g Kanechlor 400), 39 percent developed severe symptoms and an additional 49 percent developed moderate symptoms of PCB intoxication. The lowest level of PCB ingestion in an affected individual was estimated to be 0.5 g (Kuratsune, et al. 1972). Absorption via the respiratory tract and skin is also efficient as indicated by occupational exposures where effects of PCB exposure can be detected even at doses too low to produce pathology (Alvares, et al. 1977).

Distribution

PCBs given to rats by i.v. injection are removed from the blood rapidly and stored initially in the liver and muscle. With time they are redistributed primarily to skin and adipose tissue (Matthews and Anderson, 1975b). The degree to which PCBs are stored or excreted depends on their susceptibility to metabolism and, therefore, on the degree of chlorination and availability of adjacent unsubstituted carbons. Tissue levels of mono-, di-, penta- and hexachlorobiphenyls in rats given a single injected dose at 0.6 mg/kg were determined by Matthews and Anderson (1975b). The maximum doses accumulated in each tissue increased with degree of chlorination as did the half-life in each tissue. The proportion of total PCBs present in tissues as metabolites was greatest for the mono- and dichlorobiphenyls. Hexachlorobiphenyls in tissues were largely unmetabolized. The distribution of PCBs in adipose tissue provides a useful example of the relative accumulation of different isomers. Tissues were examined for up to 42 days; a summary of the results is presented in Table 6.

A similar pattern was observed in skin, with up to 22 percent of the hexachlorobiphenyl dose being accumulated there at 1 day and residual levels around 15 percent remaining at 42 days.

Single intravenous doses of 0.6 or 6.0 mg/kg of 2,4,5,2',5'-pentachlorobiphenyl were cleared from the blood in ten minutes and initially deposited in liver and muscle. They were subsequently translocated to adipose tissue and skin as depositories (Matthews and Anderson, 1975a).

A single administration of approximately 500 mg/kg of 2,5,2',5'-tetrachlorobiphenyl to rats resulted in a similar distribution with adipose, skin, and blood being the significant storage depots after 24 hours (Van Miller, et al. 1975).

The significance of chlorine position as well as number was addressed in a study of the pharmacokinetics of 3,5,3',5'-tetrachlorobiphenyl (TCB) by Tuey and Matthews (1977). The arrangement of chlorines on this molecule results in the absence of adjacent unsubstituted sites. The pattern of distribution of the compound following a single i.v. injection of 0.6 mg/kg was similar to that observed in earlier studies (Matthews and Anderson, 1975a,b) with adipose tissue and skin becoming the major long term storage sites. However, loss of 3,5,3',5'-TCB was slower than earlier observed for 2,4,5,2',5'-pentachlorobiphenyl (see Table 6) with the maximum adipose tissue load reaching 52.9 percent of total dose on

TABLE 6

Storage of PCBs in Adipose Tissue in Rats*
(Values are Percent of Total Dose 0.6 mg/kg)

Degree of Chlorination	Maximum	Time of Maximum Stored	Amount at 7 Days
mono-	11.63 ± 5.64	1 hr	0.234 ± 0.055
di-	52.75 ± 14.99	2 hr	1.837 ± 0.213
penta-	23.54 ± 3.0	1 day	13.04 ± 2.1
hexa-	85.18 ± 21.6	42 days	56.08 ± 15.72

*Source: Matthews and Anderson, 1975b

day 4 and the residual on day 7 remaining at 45.4 percent. The distribution of several tetrachlorobiphenyl isomers in mice was analyzed by Mizutani, et al. (1977). In all cases the accumulation of the compound was greater in the carcass than in the liver. A tendency for those isomers with adjacent unsubstituted carbons to be rapidly cleared was observed. 2,6,2',6'-TCB was very rapidly cleared from carcass and liver, and 2,3,2',3'-TCB was cleared fairly rapidly. However, 2,4,2',4'-TCB was more resistant to removal than 3,5,3',5'-TCB, which might not be anticipated on structural grounds. The half-life in the carcass of the former was 9.2 days but only 2.1 days for the latter. The degree of accumulation of the isomers was assessed by the introduction of an index referred to as a storage ratio (the daily amount entering storage/daily oral ingestion). By this measure 3,5,3',5'-TCB and 2,4,2',4'-TCB were similar with indices of 0.7 and 0.6, respectively, while the more readily metabolized 2,3,2',3'-TCB had an index of 0.06.

The distribution of 2,5,2',5'-TCB in infant Rhesus monkeys was determined after a single dose of tritiated TCB (500 mg/kg). At 72 hours the distribution differed from that in rats in that the label was more widely dispersed in the monkeys. Blood levels were lower than observed in rats, and the major storage depots were bone marrow, adrenal glands, and skin. Most of the labeled material was associated with macromolecules, although it was largely extractable and not covalently bound (Hsu, et al. 1975a).

Distribution of PCBs in the human body has not been the subject of systematic experimentation. Data available from general population surveys indicate that general patterns of distribution are consistent with those found in other animals. When detected in the adipose tissue of the general populace, PCB levels are around 1 mg/kg (Yobs, 1972; Kutz and Strassman, 1976; Grant, et al. 1976). Plasma levels detected in the general populace are two to three orders of magnitude lower than adipose levels (Finklea, et al. 1972). Similarly, Yusho patients exhibited a 100- to 1,000-fold greater concentration in the fat of skin, liver and in adipose tissue than in plasma. Over several years both the fat and plasma levels were observed to decline to near normal levels (Kuratsune, et al. 1976). The PCBs found in human adipose tissues in the U.S. chromatographically resemble Aroclor 1254 and 1260, suggesting that less chlorinated isomers found in Aroclor 1248 are preferentially excreted (Kutz and Strassman, 1976).

Metabolism

The metabolism of PCBs has been studied extensively in several organisms. A detailed review of PCB metabolism was written by Sundstrom, et al. (1976a). Rather than attempt to treat the subject exhaustively, this section will summarize the major characteristics of PCB metabolism which relate to their distribution, accumulation, toxicity, and possible mechanisms of carcinogenicity.

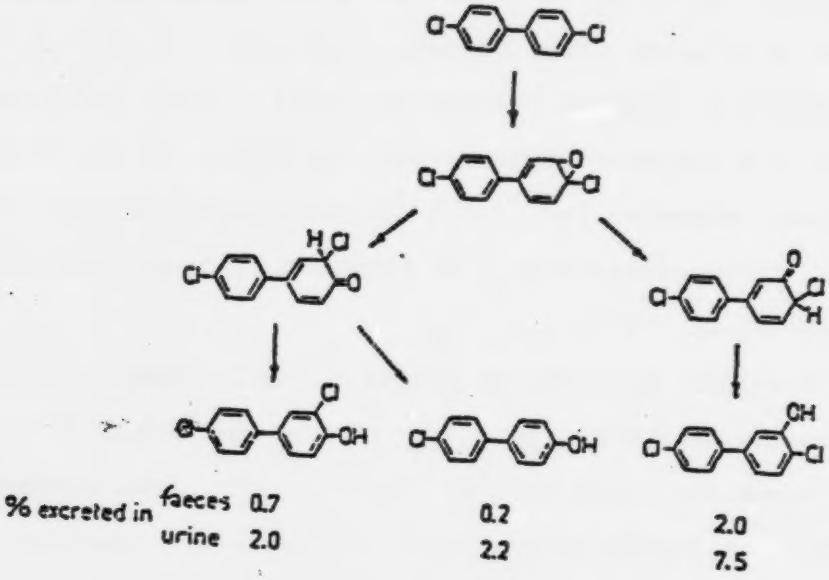
The metabolism of PCBs depends on their chlorine content and the sites of chlorination on the biphenyl (Sundstrom, et al. 1976a; Lutz, et al. 1977). While the overall mechanisms of metabolism appear to be similar in most vertebrates examined, the capacity to metabolize PCBs declines from mammals to birds to fish (Hutzinger, et al. 1972). Elucidation of PCB metabolism has been made possible by the use of individual purified isomers. Predominantly, the products of PCB metabolism at all levels of chlorination are biphenylols, biphenyldiols, and dihydrodihydroxybiphenyls, although the types and proportions of specific metabolites vary in different species. A few biphenyltriols and methoxy derivatives have also been observed (Sundstrom, et al. 1976a).

The structures of several PCB metabolites support the formation of arene oxides as intermediates. The first evidence for the formation of arene oxide intermediates was obtained by Gardener, et al. (1973). They isolated trans-3,4-dihydroxy-3,4-dihydro-2,2',5,5'-tetrachlorobiphenyl as a metabolite of 2,2',5,5'-tetrachlorobiphenyl in rabbits. More direct evidence for the formation of arene oxides was obtained by Safe, et al. (1975, 1976). In rabbits and frogs the biohydroxylation of 4-chlorobiphenyl was investigated using 4'-^{2}H-4-chlorobiphenyl. The major metabolite, 4'-chloro-4-biphenylol, retained 79 percent of the label which is consistent with arene oxide formation (Daly, et al. 1972) The subsequent isomerization of the arene oxide results in the migration of the deuterium atom from the ultimate site of hydroxylation to the adjacent carbon, an NIH shift. Daly, et al. (1972) consider the NIH shift of labeled hydrogens, halogens or alkyl substituents to be indicative of enzymatic arene oxide formation. A subsequent hydroxylation to 4'-chloro-3,4-biphenyldiol resulted in the loss of half the remaining deuterium, suggesting a direct hydroxylation rather than a second arene oxide formation (Safe, et al. 1975). 4,4'-Dichlorobiphenyl produced three metabolites in the rabbit: 4,4'-dichloro-3-biphenylol, 3,4'-dichloro-4-biphenylol, and 4'-chloro-4-biphenylol. These products are consistent with a mechanism involving 3,4-arene oxide formation followed by epoxide ring opening. Either a 1,2-halogen shift, with or without halogen elimination upon tautomerization, or 3-ol formation after arene ring cleavage would produce the ultimate products (Safe, et al. 1976; Sundstrom, et al. 1976a). The reactions are diagrammed in Figure 2. Other examples of PCBs for which metabolic pathways are consistent with arene oxide formation include 2,2',4,4',5,5'-hexachlorobiphenyl in rabbits (Sundstrom, et al. 1976b) and 4-chlorobiphenyl and 4,4'-dichlorobiphenyl in rats (Hass, et al. 1977). Infant Rhesus monkeys fed 2,5,2',5-tetrachlorobiphenyl excreted dihydroxy, dihydrodihydroxy, and dihydrotrihydroxy derivatives in urine (Hsu, et al. 1975b).

The K region epoxides of polyaromatic hydrocarbons are known to bind to nucleic acids *in vitro* (Grover and Sims, 1970) and in cultured mammalian cells (Grover, et al. 1975). Furthermore, they are capable of transforming cells in culture (Huberman, et al. 1972) although their significance in tumor induction in animals is in doubt (Grover, et al. 1975). It has been suggested that arene oxide metabolites of PCBs may react with nucleophilic sites in DNA and other macromolecules and that alkylation of critical sites may be involved in the induction of tumors (Allen and Norback, 1977).

Excretion

The primary routes of PCB excretion are bile (observed in feces) and urine. Excretion is closely coupled to metabolism. In rats less than ten percent of excreted PCBs were unmetabolized (Matthews and Anderson, 1975b). The rate and efficiency of excretion were highly dependent upon the degree of chlorination and


Cl
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H Cl
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Cl
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Cl
OH
Cl
OH
OH
Cl
Cl
% excreted in faeces 0.7
urine 2.0
0.2
2.2
2.0
7.5

FIGURE 2

Metabolic Pathways for 4,4'-dichlorobiphenyl in the Rabbit

Source: Sundstrom, et al. 1976a

structure. Urinary excretion of PCBs accounted for the removal of 59.8, 33.9, 7.6, and 0.7 percent of total dose of mono-, di-, penta-, and hexachlorobiphenyl, respectively. Over 60 percent of urinary excretion occurred within the first 24 hours and all urinary excretion ceased by the ninth and fourth days, respectively, for penta- and hexachlorobiphenyl (Matthews and Anderson, 1975b). All the 2,4,5,2',5'-pentachlorobiphenyl excreted in urine by rats was in the form of a glucuronide conjugate of a metabolite (Chen and Matthews, 1974). While urinary excretion usually ceases within a few days, biliary excretion continues for an extended period. The relative contribution of biliary excretion to the elimination of PCBs increases with chlorination. The kinetics of excretion of mono- and dichlorobiphenyl are monophasic while the elimination of penta- and hexachlorobiphenyl is biphasic. While 90 percent of PCBs up to pentachlorobiphenyl were excreted in 42 days or less, hexachlorobiphenyl was largely retained in the tissues of the animal. Extrapolation of the excretion data indicated that only 20 percent of 2,4,5,2',4',5'-hexachlorobiphenyl would ever be excreted (Matthews and Anderson, 1975b). The absence of adjacent unsubstituted carbons greatly decreased excretion as would be expected from the effects of structure on storage and metabolism. 3,5,3',5'-Tetrachlorobiphenyl (TCB) is excreted at about the same rate as 2,4,5,2',5'-pentachlorobiphenyl (Tuey and Matthews, 1977; Matthews and Anderson, 1975a). While the half-life in fat for 2,5,2',5'-TCB was about 33 hours at 500 mg/kg dose in rats (Van Miller, et al. 1975), the half-life for 3,5,3',5'-TCB was 12 to 15 days at dose levels of 0.6 mg/kg in rats (Tuey and Matthews, 1977).

The half-lives of the individual PCB isomers in the rat may be approximated by the fecal half-lives, which are 15.7 and 22.2 hours for mono- and dichlorobiphenyl, respectively. Penta- and hexachlorobiphenyls elimination is biphasic, with first and second component half-lives of 39.2 and 211 hours for pentachlorobiphenyl and 49 and 642 hours for hexachlorobiphenyl (Anderson, et al. 1977). Because only 20 percent of the hexachlorobiphenyl is ultimately excreted, its half-life is indefinite.

Rates of elimination of a series of tetrachlorobiphenyls (TCB) in mice were determined by Mizutani, et al. (1977). Half-lives for TCB isomers in liver and the carcass ranged from 0.9 days for 2,3,2',3'-TCB to 9.2 and 7.8 days for the loss of 2,4,2',4' from carcass and liver, respectively. Structure did not influence elimination as markedly as in the rat. 3,5,3',5'-TCB had half-lives of 2.1 and 2.2 days in carcass and liver. However, stimulation of metabolism by the addition of phenobarbitol did increase the rate of elimination of 2,4,2',4'-TCB more than 3,5,3',5'-TCB. The authors concluded that the rate-limiting step in the elimination of the isomers was release from storage in the tissues of the mouse rather than metabolism.

Two differences between the elimination of 2,5,2',5'-TCB in infant Rhesus monkeys and rats may be of interest in evaluating human metabolism. Single doses of 500 mg/kg to rats resulted in total elimination of about 76 percent (66 percent feces, 10 percent urine) in 72 hours (Van Miller, et al. 1975). In primates only one percent of the same dose was eliminated in feces and two percent in urine after 72 hours (Hsu, et al. 1975a). In addition, the major excreted metabolite in rats appeared to be 3-hydroxy TCB, while a dihydrodiol TCB predominated in monkeys (Van Miller, et al. 1975; Hsu, et al. 1975b).

A final comment on the pharmacokinetics of PCBs must be addressed to transplacental and transmammary movement. Transplacental uptake of PCBs by a fetus has been documented in mice (Masuda, et al. 1978), rats (Curley, et al. 1973), Rhesus monkeys (Allen and Barsotti, 1976), and humans (Yoshimura, 1974). In mice, transplacental and transmammary uptake of PCBs were approximately 0.1 to 0.2 and 20 to 35 percent of total dose, respectively (Masuda, et al. 1978). Similar values were observed in rats (Mizunoya, et al. 1974). Female monkeys consuming 2.5 ppm Aroclor 1254 transferred enough via breast milk to produce severe hyperplastic gastritis in nursing infants (Allen and Barsotti, 1976). Recently, a preliminary mathematical model of PCB distribution in rats has been proposed (Lutz, et al. 1977; Anderson, et al. 1977).

It should be noted that most of the laboratory studies discussed above have been performed with pure isomers, while toxicity studies and environmental exposures involve commercial mixtures with possible dibenzofuran contamination. In addition, commercial mixtures tend to contain asymmetrical polychlorinated biphenyls (NIOSH, 1977).

The pharmacokinetics of PCBs can be summarized with the following points:

1. They are readily absorbed through the gut, respiratory system, and skin.
2. They may initially concentrate in the liver, blood, and muscle mass; but long-term storage in mammals is primarily in adipose tissue and skin.

3. The major metabolic products of PCBs are phenolic derivatives or dihydrodiols which may be formed through pathways with arene oxide intermediates or by direct hydroxylation. The susceptibility of individual PCB isomers to metabolism is a function of the number of chlorines present on the biphenyl and their arrangement. Biphenyls which have one or more pairs of adjacent unsubstituted carbons are more rapidly metabolized than those which do not.
4. PCBs which are readily metabolized are also rapidly excreted in the urine and bile. Excretion in urine is most prominent for the least chlorinated, while bile becomes the more significant route of excretion for more highly chlorinated isomers.
5. Those isomers which are most refractory to metabolism accumulate for increasing periods of time in fatty tissues. Highly chlorinated isomers are accumulated almost indefinitely.
6. PCBs can be transferred either transplacentally or in breast milk.
7. Nonhuman primates may retain PCBs more efficiently than rodents.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Several reviews of the toxic effects of PCBs in animals and man have appeared in recent years [Kimbrough, 1974; Fishbein, 1974; Peakall, 1975; Kimbrough, et al. 1978; Cordle, et al. 1978; NIOSH, 1977 (which is particularly recommended for human effects)]. This section will attempt to highlight the most significant toxic effects observed in animals and man, but will not seek to be comprehensive.

The acute oral and dermal LD_{50}s for PCBs in rats, mice, and rabbits are given in Tables 7, 8, and 9. In the classification by the American Industrial Hygiene Association, the PCBs are slightly toxic or almost nontoxic (Hodge and Sterner, 1949). In rats, Bruckner, et al. (1973) observed a 14-day LD_{50} of 4.25 g/kg. Toxic effects of high doses of Aroclor 1242 included diarrhea, chromoacryorrhea, loss of body weight, unusual stance and gait, lack of response to pain stimuli, and terminal ataxia. CNS deterioration and dehydration were thought to be contributing factors. Histopathologic changes were observed only in liver and kidney. Miller (1944) found the guinea pig most sensitive to Aroclor 1242 followed by the rabbit and rat. In the rat, toxicity decreased with increasing degree of chlorination; however, the effect was not observed with rabbits (Fishbein, 1972).

The more significant toxic effects of PCBs are observed on repeated exposure over a period of time. Aroclor 1254 at 1,000 ppm in the diet was fatal to 75 percent of male rats in 43 days with total intakes of 500 to 2,000 mg/kg being lethal (Tucker and Crabtree, 1970). Phenoclor DP6 fed at 2,000 ppm to rats resulted in marked weight loss and death between 12 and 56 days after the initiation of treatment (Vos and Koeman, 1970). Guinea pigs treated dermally for 11 days with a total of 379.5 mg of a PCB with 42 percent average chlorine content died at intervals up to 21 days following the first application (Miller, 1944). Aroclor 1254 at 1,000 ppm in the diet killed 5/10 male rats and 8/10 female rats. At 500 ppm over eight months two males and one female died while no lethality was observed at 100 or 20 ppm. Aroclor 1260 was less

TABLE 7

Acute Toxicity of PCBs in Several Strains of Rats and Mice*

Compound Tested	Species and Sex	Route	LD g/kg Body Weight	Reference[a]
Aroclor 1254	Rat (adult, Sherman strain)	Oral	4 - 10	(5)
Aroclor 1260	Rat (adult, Sherman strain)	Oral	4 - 10	(5)
Aroclor 1254	Rat (weanling, Sherman strain)	Oral	1.295	(5)
Aroclor 1260	Rat (weanling, Sherman strain)	Oral	1.315	(5)
Aroclor 1254	Rat (female, Sherman strain)	Intravenous	0.358	(5)
Aroclor 1221	Rat (female, Sherman strain)	Oral	4.00	(6)
Aroclor 1262	Rat (female, Sherman strain)	Oral	11.3	(6)
Aroclor 1240	Rat	Oral	4.25	(7)
Aroclor 1254	Rat (Wistar, 30-day-old, M-F)	Oral	1.3	(8)
Aroclor 1254	Rat (Wistar, 60-day-old, M-F)	Oral	1.4	(8)
Aroclor 1254	Rat (Wistar, 120-day-old, M-F)	Oral	2.0	(8)
Aroclor 1254	Rat (Wistar, 120-day-old, F)	Oral	2.5	(8)
Kaneclor-400	Rat (Wistar, M)	Oral	1.30 (ml kg)	(9)
Kaneclor-400	Rat (Wistar strain, F)	Oral	1.14 (ml kg)	(9)
Kaneclor-400	Mice (CFI strain, M)	Oral	1.875 (ml kg)	(9)
Kaneclor-400	Mice (CFI strain, F)	Oral	1.57 (ml kg)	(9)
Kaneclor-300	Rat (Wistar strain, M)	Oral	1.15	(9)
Kaneclor-300	Rat (Wistar strain, F)	Oral	1.05	(9)
BP-200 biphenyls of dichloride and below	Mice (dd strain, F)	Oral	6.36	(10)
2,4'-Dichlorobiphenyl	Mice (dd strain, F)	Oral	7.86	(10)
Trichlorobiphenyl	Mice (dd strain, F)	Oral	3.06 - 4.25	(10)
Biphenyl of trichloride and below	Mice (dd strain, F)	Oral	9.27	(10)
2,4,3',4'-Tetrachlorobiphenyl	Mice (DVI strain)	Intraperitoneal	2.15	(11)
5-OH derivative of 2,4,3',4'-tetrachlorobiphenyl	Mice (CFI strain)	Intraperitoneal	0.43	(11)
2,3,4,3',4'-Pentachlorobiphenyl	Mice (CFI strain)	Intraperitoneal	0.65	(11)

[a] Reference numbers from source

*Source: Kimbrough, et al. 1978

TABLE 8

Oral LD_{50} (rat)[a,b]

Compound Tested		LD_{50} g/kg body weight
Aroclor 1221	(Undiluted)	2.000 - 3.169
Aroclor 1232	(Undiluted)	1.26 - 2.0
Aroclor 1242	(Undiluted)	0.794 - 1.269
Aroclor 1248	(Undiluted)	0.794 - 1.269
Aroclor 1260	(50% soln in corn oil)	1.26 - 2.0
Aroclor 1262	(50% soln in corn oil)	1.26 - 3.16
Aroclor 1268	(33.3% soln in corn oil)	2.5

[a] Data of Panel on Hazardous Substances (6)

[b] Source: Kimbrough, et al. 1978

TABLE 9

Skin LD_{50} (rabbits)[a,b]

Compound Tested		LD_{50} g/kg body weight
Aroclor 1221	(Undiluted)	3.98
Aroclor 1232	(Undiluted)	4.47
Aroclor 1242	(Undiluted)	8.65
Aroclor 1248	(Undiluted)	11.0
Aroclor 1260	(50% soln in corn oil)	10.0
Aroclor 1262	(50% soln in corn oil)	11.3
Aroclor 1268	(50% soln in corn oil)	10.9

[a] Data of Panel on Hazardous Substances (6)

[b] Source: Kimbrough, et al. 1978

toxic, with 8/10 females, but no males, dying at 1,000 ppm. No males died at lower doses, and 1/10 and 2/10 females died at 100 and 500 ppm, respectively. Substantial weight losses were observed at 100 and 500 ppm in both males and females (Kimbrough, et al. 1972). Mink have been shown to be unusually sensitive to PCBs. A mixture of Aroclors 1242, 1248 and 1254 at 30 ppm in the diet for 6 months was 100 percent lethal (Aulerich, et al. 1973), as was 3.6 ppm Aroclor 1254 over 105 days in another study (Plantonow and Karstad, 1973). Adult Rhesus monkeys (Macaca mulatta) were particularly sensitive to PCBs. Aroclor 1248 at 100 or 300 ppm in the diet for two to three months resulted in extreme morbidity within one month and almost 100 percent mortality within three months. Total intakes for the two groups were 0.8 to 1.0 g for 100 ppm and 3.6 to 5.4 g for 300 ppm (Allen, 1975).

The most consistent pathological changes occurring in mammals after PCB exposure are in the liver. In rats, rabbits, and guinea pigs, Miller (1944) observed fatty deposits after acute injections and similar changes in rabbits and guinea pigs after dermal application. In feeding experiments, marked fatty metamorphosis was noted in guinea pig liver with intracellular hyaline bodies being observed in rats. Less striking changes were noted in the kidneys, lungs, adrenals, and heart of guinea pigs. Rats exposed repeatedly to dietary PCBs show increased liver weights (Kimbrough, et al. 1972; Bruckner, et al. 1973). Kimbrough, et al. (1972) fed rats Aroclor 1254 or 1260 at levels between 20 and 1,000 ppm for eight months. Light microscopic changes observed included hypertrophy of liver cells, cytoplasmic inclusions, brown pigment in Kupffer cells, lipid accumulation and, at higher doses, adenofibrosis. Ultrastructural examination revealed an increase in smooth endoplasmic reticulum. The effect of Aroclor 1254 was more pronounced than that of 1260. Porphyria was observed in the livers and, occasionally, other tissues of animals exposed to either mixture.

Rats fed 2,000 ppm Phenoclor DP6 also had enlarged livers with vacuolated foamy cells containing pycnotic nuclei (Vos and Koeman, 1970). Vacuolization of liver cells was also noted by Bruckner, et al. (1973) after dosing rats with 100 mg/kg Aroclor for three weeks, although no overt toxicity was manifest.

Rats fed 100 ppm Aroclor 1242 (6.6 to 3.89 mg/kg/day) or Aroclor 1016 (6.9 to 3.5 mg/kg/day) for periods of up to ten months showed no signs of overt intoxication or gross liver changes. Enlarged hepatocytes with vacuolated cytoplasms and inclusions were noted. Aroclor 1242 seemed to produce more pronounced changes than 1016. Four and six months after the discontinuation of exposure hepatocytes were still enlarged but cytoplasmic vacuoles and inclusions had diminished, suggesting a degree of reversibility of effect. Significant residual levels of PCBs remained in adipose tissue. Using electron microscopy, increased smooth endoplasmic reticulum and lipid vacuoles as well as atypical mitochondria were observed. No significant gross changes in other organs were noted (Burse, et al. 1974).

Allen and Abrahamson (1973) fed rats 1,000 ppm of either Aroclor 1248, 1254, or 1262 for 1, 3, 7, 14, 21, or 28 days or 6 weeks. Overt toxicity was not observed, although weight gain was retarded in all treated groups. The effect was inversely proportional to percent chlorination. Increased liver size, protein, and RNA content were observed. The magnitude of changes increased with the percent chlorination. Hypertrophy was associated with proliferation of the smooth endoplasmic reticulum, formation of membranous arrays, and increased lipid droplets.

The effect of metabolism on toxicity was explored by giving rats large (1.5 g/kg) single doses of 2,5,2',5'-tetrachlorobiphenyl which produced high mortality within two to three days (Allen, et al. 1975). Pretreatment with phenobarbitol to induce metabolic enzymes allowed survival without obvious ill effects following a 1.25 g/kg dose, while treatment with the microsomal enzyme inhibitor SKF 525A lead to 100 percent mortality in four days. The ability to metabolize and eliminate 2,5,2',5'-TCB appears to protect the animal. Dietary administration of 100 ppm 2,5,2',5'-TCB for three weeks produced less liver hypertrophy than Aroclor 1248.

Liver pathology in mice exposed to 1.5 mg PCB/day was essentially the same as seen in rats, including increased smooth endoplasmic reticulum and increased lipid droplets (Nishizumi, 1970).

Rabbits receiving 300 mg orally of Aroclor 1221, 1242, or 1254 for 14 weeks were examined (Koller and Zinkl, 1973). Aroclor 1221 and 1242 treated rabbits gained weight at control rates while 1254 treated rabbits did not gain as much. Livers of 1254 and 1242 treated animals were enlarged while livers of 1221 treated animals were smaller than controls. Gross liver lesions and small uteri were apparent in the 1254 treated animals but not the others. Liver pathology in 1254 treated animals included enlarged hepatocytes with foamy to granular cytoplasms and subcapsular midzonal necrosis. Aroclor 1242 produced a liver pathology similar to 1254. Aroclor 1221 treated animals were free of histologic changes.

Dermal studies with rabbits using Clophen A60, Phenoclor DP6, and Aroclor 1260 indicated that the last was the least toxic (Vos and Beems, 1971). The former two mixtures had been shown to be contaminated with tetra- and pentachlorodibenzofuran (Vos, et al. 1970). Skin lesions produced included hyperplasia and hyperkeratosis of the epidermal and follicular epithelium and were accompanied by pathological changes in the liver and kidney. The chlorodibenzofuran impurities in the PCBs were thought to be responsible for the skin lesions. A comparison of the toxic effects of dermally applied 2,4,5,2',4',5'-hexachlorobiphenyl and Aroclor 1260 demonstrated that the skin lesions appeared sooner and were more severe after treatment with the commercial mixture. Liver changes were found in both treatment groups with the pure isomer inducing the more severe effects. From this study it was concluded that the chlorodibenzofuran contaminants in commercial mixtures probably contribute to the skin lesions (chloracne), edema formation, and liver damage. PCBs contribute in lesser degrees to chloracne and liver damage but are primarily responsible for the hepatic porphyria observed in PCB intoxication (Vos and Notenboom-Ram, 1972).

Nonhuman primates are rather sensitive to PCBs. Male Rhesus monkeys were fed 300 ppm Aroclor 1248 for three months. Effects which began to appear within a month included hair loss, subcutaneous edema, purulent discharge from the eyes, acneform eruptions, and liver hypertrophy caused by smooth endoplasmic reticulum proliferation. Marked hypertrophy of the gastric mucosa was a significant finding not usually seen in rodents. Invasion of the submucosa by the mucosal epithelium with increased cellularity and dysplasia occurred in the stomach. The dietary levels used were about 10-fold greater than the contamination levels in foods during the early 1970's, and the gastric changes observed were considered to be of particular significance to human risk (Allen and Norback, 1973). When fed low levels (2.5 and 5 ppm) of Aroclor 1248 for 52 weeks female monkeys developed periorbital edema, alopecia, erythema and acneform lesions. Effects in males were less pronounced (Barsotti and Allen, 1975). The high sensitivity of monkeys to PCBs has been confirmed and the evaluation of the toxic effects, particularly in the gastric mucosa, has been extended (McNulty, 1976; Bell, 1976). The pathologic effects of PCBs in nonhuman primates have been reviewed by Allen and coworkers (Allen, 1975; Allen and Norback, 1976).

The ability of PCBs to induce liver microsomal enzymes was demonstrated by Street, et al. (1969). Enzyme induction by commercial PCBs has been shown in rabbits (Villeneuve, et al. 1971a), rats (Litterst and VanLoon, 1972), and primates (Allen, et al. 1974b). In rats induction is observed following intraperitoneal injection (Bickers, et al. 1972) or skin application (Bickers, et al. 1975). Dietary threshold values for enzyme induction vary between 0.5 and 25 ppm (Villenueve, et al. 1971a; Litterst, et al. 1972; Turner and Green, 1974). The induction of demethylating activity in rats by Aroclor 1254 was maximum in seven days while cytochrome P450 and nitroreductase activities continued to rise over four weeks of treatment. Activities declined slowly after discontinuation of treatment, reaching control levels in about ten days (Litterst and VanLoon, 1974). Cutaneous exposure to PCBs resulted in a maximum induction within two to six days (Bickers, et al. 1972, 1975). Degree of induction of enzyme activities was found to correspond to increasing chlorine content of Aroclors (Litterst, et al. 1972) and of di-, tetra-, and hexachlorobiphenyl mixtures (Schmoldt, et al. 1974). The effects of chlorine content and position of pure isomers were examined by Johnstone, et al. (1974), Ecobichon (1975), and Ecobichon and Comeau (1975). More highly chlorinated isomers and those substituted at the 4 and 4' positions were most active in inducing enzymes associated with the endoplasmic reticulum. For less localized enzymes, position was less critical, although chlorinated compounds were more effective than biphenyl.

The effects of dietary exposure to Aroclor 1254 on enzyme induction were investigated in rats by Bruckner, et al. (1977). Aroclor 1254 at 5 or 25 ppm induced dose-dependent increases in the metabolism of pentobarbitol, aminopyrine, and acetanilide after 35, 70, and 140 days of exposure. Exposure to 1 ppm had little effect on metabolism. Liver weight and serum triglyceride levels were elevated only in animals exposed to 25 ppm. In 15-day experiments induction of aminopyrine N-demethylation was observed after the first day of exposure at 5 and 25 ppm, and acetanilide hydroxylation was induced after two days. Aminopyrine N-demethylation returned to normal 15 days after the termination of exposure. Consumption of as little as 1 to 2 mg of PCBs in 24 hours was sufficient to stimulate acetanilide hydroxylation.

Commercial PCBs have been shown to induce cytochrome P450 (phenobarbitol type) and cytochrome P448 (3-methylcholanthrene type) (Alvares, et al. 1973). More recent studies with purified isomers indicated that ortho-para-substituted PCBs induce P450 while meta-para-substituted PCBs induce P448. Substitution in the ortho-position dominates over meta-, and no isomers were found to induce both activities (Goldstein, et al. 1977). The induction of both systems by commercial preparations and some purified isomers has recently been shown to result from contamination with dibenzofurans. Even "99 percent pure" isomeric PCBs containing 44 ppm tetrachlorodibenzofuran effectively induces P448 while more rigorously purified material does not (Goldstein, et al. 1978). This observation serves as a reminder that the effects of trace contaminants must be kept in mind when evaluating the toxic effects of PCBs.

Enzyme inducing effects of PCBs have also been examined *in vivo* by the observation of shortened phenobarbitol sleeping times in PCB-treated animals (Bickers, et al. 1972; Johnstone, et al. 1974; Villeneuve, et al. 1972). PCB induction of enzyme activities in other tissues has included skin (Bickers, et al. 1975), placenta and fetus (Alvares and Kappas, 1975), neonatal liver during lactation (Alvares and Kappas, 1975), and lung and kidney (Vainio, 1974).

Other systemic effects of PCBs in mammals include porphyria (Bruckner, et al. 1974), increased thyroxin metabolism (Bastomsky, 1974) and ultrastructural changes in the thyroid (Collins, et al. 1977), inhibition of ATPases (LaRocca and Carlson, 1975), and interference with oxidative phosphorylation (Sivalingan, et al. 1973). Alterations in steroid hormone metabolism are produced by PCBs in rats (Bitman and Cecil, 1970), mice (Orberg and Kihlstrom, 1973), and other animals. Aroclor 1254 appears to reduce liver vitamin A concentrations in pregnant rabbits (Villeneuve, et al. 1971b). A more complete review of these effects can be found in Matthews, et al. (1978).

PCBs have been shown to have immunosuppressive effects in rabbits (Vos and Beems, 1971; Street and Sharma, 1975), guinea pigs (Vos and van Genderen, 1973; Vos and DeRoij, 1972), monkeys, mice (Thomas and Hinsdill, 1978), and several birds. Significant effects were observed in Rhesus monkeys exposed to dietary levels of Aroclor 1248 as low as 5.0 ppm.

Effects of Aroclor 1254 and 1260 on reproduction in Sherman strain rats were investigated (Linder, et al. 1974). Dietary levels of 5 ppm Aroclor 1254 had no effect on reproduction in rats exposed through two generations. Liver weights were increased in male and female offspring of the F_1 and F_2 generations. At 1 ppm, Aroclor 1254 caused increased liver weights in F_1 male weanlings. With Aroclor 1254 at 20 ppm, the number of pups in the F_{1b} and F_2 generations was reduced, while 100 ppm resulted in increased mortality in F_{1b} offspring and decreased the mating performance of F_{1b} adults. Aroclor 1260 produced increased liver weights in F_1 offspring at 5 ppm but did not affect reproduction at 100 ppm. At 500 ppm litter sizes were reduced and survival was decreased in F_1 litters. Pregnant rats given 100 mg/kg/day Aroclor 1254 on days 7 to 15 had grossly normal litters but only 30.1 percent survived to weaning. Dosage rates of 50 mg/kg/day Aroclor 1254 or 100 mg/kg/day Aroclor 1260 did not affect reproduction or pup survival.

Rabbits fed 0.1 or 1.0 mg/kg body weight Aroclors 1221 or 1254 showed no significant decrease in number of pregnancies or number of fetuses per litter (Villeneuve, et al. 1971a). No induction of fetal liver enzymes could be detected. However, administration during gestation of 600 to 2,500 ppm Aroclor 1254 in the diet resulted in resorptions, abortions, maternal death, and asymmetric skulls in two fetuses (Villeneuve, et al. 1971b).

Reproductive effects in mice were investigated in animals treated for ten weeks with 0.025 mg/day Clophen A60 (Orberg and Kihlstrom, 1973). The length of the estrus cycle was increased from 6.6 days in controls to 8.7 days in experimental animals. Also, the percentage of implanted ova was reduced from 87.0 to 79.5. In a second study the reproductive effects of neonatal exposure to PCBs in milk were examined by injecting lactating female mice with Clophen A60. On the day of parturition and at weekly intervals for three weeks, the females were injected with 50 mg of PCB. When treated male and female offspring were mated with each other, the percent implantation dropped from a control level of 94 percent to 75 percent (Kihlstrom, et al. 1975).

In female Rhesus monkeys exposure to 25 ppm Aroclor 1248 in the diet for two months lead to the typical effects of PCB intoxication for monkeys including edema, alopecia, and acne. One animal ingesting a total of 450 mg PCB died two months after exposure ended and was found to have hyperplastic gastritis and bone marrow hypoplasia. The remaining five animals were bred three months after treatment. Three were thought to have conceived but resorbed or aborted the embryos in the first two months of pregnancy. One delivered a fully developed but small infant (Allen, et al. 1974b).

In a more developed study both male and female Rhesus monkeys were fed either 2.5 or 5.0 ppm Aroclor 1248 in the diet (Barsotti and Allen, 1975; Barsotti, et al. 1976). The total intake in the first six months for the females was 180 and 364 mg for the 2.5 and 5.0 ppm diets, respectively. Untreated females bred to treated males had normal rates of conception (Barsotti and Allen, 1975). Treated females bred to normal males produced the following rates of conception: control, 12/12; 2.5 ppm, 8/8; 5.0 ppm, 6/8. Live births resulting from the conceptions were: control, 12/12; 2.5 ppm, 5/8; 5.0 ppm, 1/6. In the 2.5 ppm group, three fetuses were resorbed shortly after conception. In the 5.0 ppm group, three pregnancies aborted at 46, 67, and 107 days of gestation, one fetus was resorbed, one was stillborn, and one normal birth occurred. The two females who failed to conceive were subsequently bred five times without conception. The live born infants were of low birth weight and showed signs of PCB intoxication after nursing their mothers for less than two months. Three infants died 44 to 112 days after birth (Barsotti, et al. 1976). The mothers' breast milk contained 0.154 to 0.397 ppm PCBs and one contained 16.44 ppm (fat basis) (Allen and Barsotti, 1976). It should be noted that the dose levels producing these rather striking effects are within the range of contamination of the human diet observed until the mid-1970's.

Recently, adipose tissue levels of PCBs in infant Rhesus monkeys exposed in utero and via breast milk have been correlated with behavioral effects (Bowman, et al. 1978). Three of five infants born to mothers exposed to 2.5 ppm Aroclor 1248 in the diet during pregnancy and lactation survived over four months. PCB levels in fat tissue in the infants declined with a first order rate constant over a period of 8 to 23 months of age. Extrapolated maximum PCB levels were 21, 114, and 123 µg/g fat. A battery of 11 behavioral tests was conducted with the three exposed animals and four controls over this time period and a positive correlation between reduced performance and PCB body burden was observed for seven tests.

Minks have been found to be exceedingly sensitive to PCB-induced reproductive failure. A marked increase in kid mortality was observed in commercial mink in the mid-1960's after fish meal derived from spawning Great Lakes Coho salmon was incorporated into the diet. Laboratory studies confirmed that the reproductive losses were related to the ingestion of Great Lakes fish (Aulerich, et al. 1971), and subsequent investigation showed that PCBs contaminating the fish meal were the probable toxic agents (Ringer, et al. 1972). When fed 10 ppm each of Aroclors 1242, 1248, and 1254 (30 ppm total), all 11 adult female mink died prior to the end of the normal whelping (delivery) period (Ringer, et al. 1972). Aroclor 1254 fed at 10 ppm resulted in no offspring among six females. At 5 ppm, Aroclor 1254 fed for four months prior to whelping depressed reproduction with only 3 of 12 females whelping and 3 of 9 kits born alive. At 1 ppm Aroclor 1254, 8 of 10 females whelped and

35 of 43 kits were born alive. Among control animals all 11 whelped and 56 of 66 pups were alive at birth. The reproductive toxicity of Aroclor 1254 becomes pronounced between 1 and 5 ppm in the diet (Ringer, et al. 1972). At 2 ppm in a nine month feeding trial, Aroclor 1254 significantly reduced reproduction while Aroclors 1016, 1221, and 1242 did not (Aulerich and Ringer, 1977). Assuming a food intake of 150 gm/day (Schaible, 1970), the total PCB intake in the two trials would have been 90 mg at 5 ppm for four months or 61 mg at 2 ppm for nine months (Aulerich and Ringer, 1977).

Human exposures to PCBs resulting in toxic effects have almost all resulted from the ingestion of rice oil contaminated with Kanechlor 400 in Japan or from industrial exposure. While absorption through the gut was the route of exposure in the former case, occupational exposures occur largely by inhalation or absorption through the skin.

Yusho, the disease resulting from the ingestion of contaminated rice oil in Japan, has been the subject of continuing study since the episode of exposure in 1968. Periodically, special reports on these continuing studies have been published in Fukuoka Acta Medica. These results, largely published in Japanese, have been reviewed in English by the Japanese investigators both early in the study (Kuratsune, et al. 1972; Kuratsune, 1972) and more recently (Kuratsune, et al. 1976). The cause and scope of the exposure of the Japanese public has been described above (see Ingestion from Food section). The initial symptoms of Yusho included increased eye discharge and swelling of upper eyelids, acneform eruptions and follicular accentuation, and pigmentation of the skin. Other symptoms including dermatologic problems, swelling, jaundice, numbness of limbs, spasms, hearing and vision problems, and gastrointestinal disturbances were prominent among the complaints of patients seen within the first eight months after exposure (Kuratsune, et al. 1972). The first patients were seen almost immediately after the release of the contaminated oil in February 1968. Of a group of patients seen between October 1968 and January 1969, 55 percent became ill between June and August. It was ultimately determined that as many as 63.9 percent of those who consumed contaminated oil became ill. Among a group of 146 known users of the oil, 80 consumed less than 720 ml, and 88 percent of these users were affected. Among those who used more than 720 ml, 100 percent were affected. The clinical severity of symptoms did not differ by sex, but the age group 13 to 29 was more affected than others (Kuratsune, et al. 1972).

The analysis of the oil indicated that it contained between 2 and 3 mg/kg of Kanechlor 400 (Kuratsune, et al. 1972). It was later discovered that Kanechlor 400 contained 18 ppm of polychlorinated dibenzofurans (PCDFs) and that the PCDF concentration in "Yusho Oil" was about 5 ppm (Nagayama, et al. 1975). The PCDF level in the oil was 250 times greater than would be expected based on the level in fresh Kanechlor 400, leading Kuratsune, et al. (1976) to suggest that the concentration increased with PCB use as a heat transfer medium.

The amounts of Kanechlor 400 ingested were estimated for the original 146 person study group. The average amount ingested was estimated to be 2 g while the minimum amount ingested by a patient was about 0.5 g (Kuratsune, et al. 1972).

Laboratory evaluations of patients during the early period were summarized by Kuratsune (1972). Several changes in blood were noted, including decrease in erythrocyte count, increase in leukocyte count, and increase in serum lipids, particularly triglycerides. Blood proteins, electrolytes, and enzyme activities were normal in most instances. Some increases in urinary ketosteroid excretion were observed. The "cheesy" material from Yusho acne contained more steric and oleic acids than did "normal acne," but less myristic palmitic and palmitoleic acid. Linoleic acid was present in Yusho acne but not "normal acne." Liver biopsy indicated hypertrophy of the smooth endoplasmic reticulum, reduction of the rough endoplasmic reticulum, filamentous inclusions, and mitochondrial abnormalities. Skin changes included hyperkeratosis, cystic dilatation of the hair follicles, and marked increase of melanine in basal cells of the epidermis. Decreased sensory nerve conduction velocities were observed in 9 of 23 patients. Abnormalities of the eyes included hypersecretion of the meibomian gland and abnormal pigmentation of the conjunctiva.

Thirteen women, 11 with Yusho and 2 without, but married to men with Yusho, delivered 10 live and 2 stillborn infants between February 15 and December 31, 1968. Nine of the 10 had grayish-dark stained skin, and 5 had similar pigmentation of the gingiva and nails. Eye discharge was common. A stillborn fetus had marked hyperkeratosis, atrophy of the epidermis, and cystic dilatation of the hair follicle. Increased melanin pigment in the blood cells and the epidermis was also noted. Twelve of the 13 fetuses were small for date of birth. The growth of children affected by Yusho was significantly lower than Japanese national standards. A detailed clinical study of four Yusho babies showed that they were small for their age, had dark pigmentation on skin and mucous membranes, and gingival hyperplasia. Teeth were erupted at birth; spotted calcification of the parieto-occipital skull, wide fontanels, and saggital suture were present, along with facial edema and exophthalmic eyes (Yamashita, 1977).

By three years after the episode about half the patients were improving while 40 percent were essentially unchanged and 10 percent were becoming more severely affected. Even among those said to be improving, many still complained of persistant headaches, general fatigue, weakness and numbness of limbs, weight loss, and other problems (Kuratsune, et al. 1972).

An evaluation of the longer term effects of Yusho has been summarized by Kuratsune, et al. (1976). In 1972 Masuda noted a peculiar gas chromatographic pattern of PCB fractions which was common to blood, tissues and breast milk of Yusho patients (Koda and Masuda, 1975). A pattern seen in about 60 percent of Yusho patients contained a larger amount of a late eluting peak than PCB-containing tissues resulting from other types of exposures. This pattern was referred to as type A. A similar pattern seen in about 37 percent of Yusho patients was referred to as type B. These two patterns (types A and B) have never been observed in individuals (human or animal) exposed to PCBs in other situations. These types appear unique to Yusho. Tissue levels of PCBs in patients undergoing surgery or who died and were autopsied were followed over several years. Adipose tissue levels were high (13 to 76 ppm) shortly after the end of exposure but were substantially lower by the next year. By 1970 and beyond, tissue levels were within the normal range in the cases studied. Blood levels were not determined until 1972 by which time they were in the normal range. Patients whose plasma PCB pattern was type A had higher levels than those with type B.

The discovery of substantial levels of PCDF in Yusho oil has been discussed. Levels of PCDFs in control individuals and Yusho patients were determined. No detectable (0.1 ppb) PCDFs were found in controls while tissues of patients who died in 1969 and 1972 contained 0.009 and 0.013 ppm in adipose and liver respectively. Ratios of PCB/PCDF were 144 and 4 for adipose tissue and liver, respectively. PCDF levels were higher in liver than adipose on a fat basis. Although the sample was small, the levels in whole adipose tissue appeared to have dropped to about one-third of the 1969 level by 1972.

By 1972, the dermal and mucosal signs which were most marked in the initial stages of toxicity were gradually improving. Symptoms considered to be due to internal disturbances, such as fatigue, poor appetite, abdominal pain, headache, pain and numbness in the limbs, and cough and expectoration of sputum, have become more prominent. Between March 1973 and April 1974, 79 patients were examined and blood PCBs evaluated (Koda and Masuda, 1975). Of patients with type A or B plasma PCB chromatographic patterns, a majority exhibited some or all of the typical spectrum of dermatological symptoms, with frequencies in type A patients being higher than in type B patients. Because PCB levels in type A patients were higher than in type B, the severity of symptoms was correlated with blood PCB levels.

Serum triglyceride levels in males did not decline significantly between 1969 and 1974 (Okumura, et al. 1974). Levels in female patients declined but were still above normal. The elevation of triglycerides correlated with increased blood PCB levels and the type A pattern.

Serum bilirubin in patients was lower in 121 patients than in 257 controls, indicating an accelerated rate of disposal (Hirayama, et al. 1974).

Long-term effects continued to be observed in children born to Yusho mothers. Nine infants with dark brown skin pigmentation were born to Yusho mothers between 1969 and 1972, three of them to a patient between 1969 and 1971 (Yoshimura, 1974). The plasma PCB levels of 30 children born to 18 Yusho mothers were significantly above control levels but lower than maternal levels (Abe, et al. 1975). Children nursed by their mothers had higher levels than children who were not breast fed. One case was reported by Yoshimura (1974) in which a baby was thought to have acquired Yusho solely as a result of breast milk intake.

Masuda, et al. (1974) found PCB levels in breast milk of five Yusho women between 0.03 and 0.06 ppm, which was just within the normal range. A recent study of PCB levels in the breast milk in 400 Japanese women detected average levels of 0.033, 0.026, and 0.029 ppm in three measurements made at two month intervals (Yakushiji, et al. 1977). Based on these levels, they calculated that daily intake by a nursing infant would be 24 μg/day. This can be compared to an average dietary intake by Japanese adults of 21 µg/day or 9 µg/day by U.S. adults. By April 30, 1975, 29 of 1,291 Yusho patients had died. Among 22 who died before September, 1973, nine deaths resulted from malignant neoplasms (Urabe, 1974).

The occurrence of Yusho symptoms after modest PCB intake coupled with the similarity of many of the symptoms to those seen in animals, particularly primates, suggests that the toxic effects observed in animals must be considered potentially accurate models for humans. The persistence of symptoms in Yusho patients is a particular source of concern. The major uncertainty regarding toxicity in Yusho patients rests with the unknown effects of the PCDFs present in unusually high concentrations in Yusho oils.

Early reports of toxic effects of occupational PCB exposure are not easily interpreted because a mixture of compounds including chloronaphthalenes was present. A fatal case resulted from exposure to a mixture of 90 percent chloronaphthalenes and 10 percent PCBs (Drinker, et al. 1937). The subject developed chloracne, followed by jaundice and abdominal pain, and was found to have cirrhosis of the liver at autopsy.

Many studies of occupational exposure have shown varying degrees of toxicity under different conditions. The following discussion will highlight studies which indicate the types of toxic reactions commonly observed in occupational exposures and the levels of sensitivity in different situations. A detailed review of occupational exposure to PCBs has recently been prepared (NIOSH, 1977).

Elkins (1959) found that average PCB concentrations in the workroom air of several plants in Massachusetts ranged from 0.1 to 5.8 mg/m^3 while peak concentrations were between 0.2 and 10.5 mg/m^3. Immediate toxic effects were not seen; however, exposure to 10 mg/m^3 was said to be unbearably irritating. Three cases of severe chloracne were reported in a work environment in which PCB air levels were found to be between 5.2 and 6.8 mg/m^3. The workers developing chloracne had been exposed for 2 to 4 years. Alterations in liver function or other abnormalities were not found (Puccinelli, 1954).

An analysis of the health effects of PCBs on eight laboratory workers involved in testing dielectric fluids was made by Levy, et al. (1977). The workers, all males 25 to 49 years of age, had been employed 2.5 to 18 years. Breathing zone, point source, and general work area samples were collected on three occasions. The ranges observed were: breathing zone, 0.014 to 0.073 mg/m^3; point source (near an oven), 0.042 to 0.264 mg/m^3; and room area, 0.013 to 0.15 mg/m^3. Blood PCB concentrations were 36 to 286 ppb which is substantially above the range in several studies of general populations (Finklea, et al. 1972). Workers complained of dry sore throat (6/8), skin rash (3/8), gastrointestinal disturbances (3/8), and eye irritation and headache (2/8). Examination disclosed one patient with skin rash, two with nasal irritation, one showing rales, and four with high blood pressure, but no abnormalities in liver function.

Toxic effects from a low-level exposure were reported by Meigs, et al. (1954). A leaking heat exchanger in a chemical plant discharged PCB vapors. No employees worked routinely at the point of leakage, but breathing zone levels in work areas were found to be 0.1 mg/m^3. The period of exposure was 19 months. Seven of 14 exposed workers developed mild to moderate chloracne after exposure durations of 5 to 14 months. Liver function tests showed normal serum bilirubins, 24- and 48-hour cephalin flocculations, thymol turbidities, and serum alkaline phosphatase activities in six of the seven workers, but borderline increases in cephalin flocculation and thymol turbidity in the seventh. After 13 months, the thymol turbidity but not the cephalin flocculation had improved.

A study of PCB exposure in six Japanese industrial plants has been reported (Hasegawa, et al. 1972; Hara, et al. 1974, 1975). Although the original publications are in Japanese, a detailed description in English is available (NIOSH, 1977). PCBs were manufactured in one plant, used in manufacturing capacitors in four plants, and had been used in a fifth plant until one month before the study began. The sixth plant used biphenyls, not PCBs. PCB concentrations in air as both vapor and particulates were determined. The lowest levels in one plant were 13 to 15 µg/m^3 vapor and 4 µg/m^3 particulate while the highest levels in a single plant were 95 to 965 µg/m^3 vapor, 73 to 650 µg/m^3 particulate. Except in the instance of a spill, vapor concentrations always exceeded particulate concentrations. Blood PCB levels in 99 workers were found to average 370 ppb as compared to values in 20 controls averaging 20 ppb. A correlation between duration of exposure and blood level could not be found in data from three of the plants. Dermal effects found were chromodermatosis of the dorsal joints of the hands and fingers and of the nail bed, and acneform exanthema. Dermal effects seemed unrelated to blood levels, suggesting that they resulted directly from skin contact. Changes in fat metabolism and mild disturbances in liver function were found. The consequences of termination of PCB exposure were examined by following 38 current and 80 former workers from 1972 to 1975 who were from the plant which had discontinued PCB use. During the period of PCB exposure, 17 capacitor immersion process workers had blood levels of 7 to 300 ppb, which were closely related to years of exposure. One year after cessation of exposure, blood PCB levels decreased but not uniformly. The average decrease was about 75 percent of the original value. The blood half-lives of PCBs were determined and found to be related to the number of years of exposure. For one year of exposure, $T_{1/2}$ = 3 months, while for 10 to 15 years exposure, $T_{1/2}$ = 30 months. The investigators concluded that blood served only as a PCB carrier while fat served as the depot tissue. Many of the employees complained of blackheads, acne, and skin irritation while working with PCBs; however, these conditions cleared markedly after exposure ceased. Serum triglyceride levels in workers were elevated in correlation with blood PCB levels.

A study in Australia by Ouw, et al. (1976) examined two groups of workers with different levels of exposure in a capacitor manufacturing facility. One group (inside) worked in an impregnation process where exposure to heated (70°C) Aroclor 1242 occurred. The second group (outside) assembled cool Aroclor-dipped components in a location separate from the first group. The entire group had an average blood PCB level near 400 ppb. The distribution of individual Aroclor components differed between the groups with the outside workers being low in early eluting (on gas chromatography) fractions but elevated in late eluting fractions relative to the inside group. Abnormalities in liver function were not observed but skin irritation and eczematous rashes were observed. One worker had chloracne but no systemic effects. The severity of dermal effects was not clearly correlated to blood PCB level. Breathing zone air concentrations in the impregnation room varied from 2.22 to 0.32 mg/m^3. To bring conditions within government guidelines, improved exhaust ventilation was installed and workers were encouraged to wear impervious gloves to reduce skin absorption. These actions reduced atmospheric PCB levels to 0.75 to 0.08 mg/m^3. After two months, new blood samples were taken which indicated that a slight increase in blood levels had occurred. Failure to wear gloves was the reason cited for the failure to improve blood levels.

A recent study of liver function in Aroclor 1016-exposed workers illuminates the sensitivity of the liver to exposure (Alvares, et al. 1977). Antipyrene clearance was determined in five workers who had been occupationally exposed to PCBs for at least four years and Aroclor 1016 for at least two years. None of the workers showed any manifestations of PCB toxicity. When compared to five controls matched for sex, age, and smoking and drinking habits, the antipyrene half-life was about two-thirds of the control level (10.8 ± 0.7 experimental vs. 15.6 ± 1.0 control). The increased rate of antipyrene clearance was taken to be an indication of higher levels of metabolic enzymes in the livers of the exposed workers.

Data from this limited review of occupational studies indicate that symptoms much like those seen after PCB ingestion can occur after atmospheric or dermal exposure. Air PCB concentrations as low as 0.1 mg/m^3 can produce toxic effects (Meigs, 1954) and exposure to levels producing no overt toxicity can affect liver function (Alvares, et al. 1977). Recovery after termination of exposure occurs but is slow and depends upon the amount of PCBs stored in adipose tissue (NIOSH, 1977).

Synergism and/or Antagonism

It appears that the synergistic antagonistic effects of PCBs result from their ability to induce mixed function oxidases in liver and other tissues, although the effects of the accelerated metabolism of drugs, such as phenobarbitol or hormones, such as ketosteroids and thyroxin, have been discussed above. The consequences of the PCB induced metabolism of carcinogenic agents such as benzene hexachloride or aflatoxin will be discussed below in the section on carcinogenicity.

Teratogenicity

The reproductive effects of PCBs in animals and man have been discussed above. It is clear that PCBs readily cross the placental barrier and accumulate in fetal tissues. Primate infants exposed to PCBs *in utero* are typically retarded in growth during gestation (Barsotti and Allen, 1975), and reproductive failures (abortions, stillbirths) are common (Linder, et al. 1974). Live born animal and human infants often display symptoms of toxicity common for the species (Kuratsune, et al. 1976; Linder, et al. 1974). However, indications of structural malformations or genetic changes have been rare. Villeneuve, et al. (1971b) noted asymetric skull formation in two rabbit fetuses exposed to high levels of Aroclor 1254 *in utero*. A written communication by F.L. Earle (as cited in NIOSH, 1977) reported unspecified terata in canine pups born to females exposed to 48 or 200 ppm but not 20 ppm dietary equivalent, and in piglets from sows fed the equivalent of 50 ppm. No additional information was given.

Mutagenicity

The mutagenicity of different PCB preparations has been evaluated in several test systems. The single isomer 4-chlorobiphenyl was found to be highly mutagenic in *Salmonella typhimurium* strain TA1538 after liver microsomal enzyme activation (Wyndham, et al. 1976). The products formed under these activation conditions were 4-chloro-4'-biphenylol and 4'-chloro-3,4-biphenyldiol, which, as previously discussed, are indicative of arene oxide formation (Safe, et al. 1975). In the same study, Aroclor 1221 was less mutagenic while Aroclor 1254, 1268 and 2,5,2',5'-tetrachlorobiphenyl were essentially inactive. Mutagenic activity decreased with increasing chlorination.

Recent attempts to repeat the experiment with different cultures of the same tester strain have not detected any mutagenic activity (S. Safe, personal communication).

Also, 4-chlorobiphenyl was toxic but not mutagenic to *S. typhimurium* TA1538 with or without activation by Aroclor 1254 (S. Rinkus, personal communication). 4-Chlorobiphenyl has been shown to induce unscheduled DNA synthesis, an indication of DNA repair, in Chinese hamster ovary cells (S. Safe, personal communication).

The Japanese Ministry of Health and Welfare-supported mutagenicity screening program investigated Kanechlors 300 and 500 (Odashima, 1976). Both compounds were negative in the Salmonella system but Kanechlor 300 was listed as positive in a bacterial DNA repair assay and a cytogenetic analysis with Yoshida sarcoma cells. Kanechlor 500 was positive in a mouse bone marrow cell cytogenetic analysis.

Heddle and Bruce (1977) reported Aroclor 1254 as negative in S. typhimurium, the micronucleus test, and a sperm morphology assay. Aroclor 1254 administered to rats at 50 mg/kg/day for seven days produced no chromosomal abnormalities in sperm (Dikshith, et al. 1975).

The effects of Aroclor 1254 and 1242 on bone marrow cells were evaluated in Osborne-Mendel rats (Green, et al. 1975a). Animals in groups of eight were given single doses of Aroclor 1242 at 1,250, 2,000, or 5,000 mg/kg or multiple doses of 500 mg/kg/day for four days. Aroclor 1254 was given for five days at 75, 150, or 300 mg/kg/day. Aroclor 1242 was more toxic than 1254. Mitotic indices were not reduced by Aroclor 1242 treatment and no increase in chromosomal abnormalities was observed. Aroclor 1254 reduced the mitotic index of bone marrow cells at 150 and 300 mg/kg/day but not at the low dose. Again, no increase in chromosomal abnormalities was seen. Cytogenetic abnormalities were found in spermatogonial cells of animals treated at 5,000 mg/kg or 500 mg/kg/day Aroclor 1242 but not in statistically significant numbers.

A dominant lethal test with Aroclor 1242 and 1254 was also performed in Osborne-Mendel rats (Green, et al. 1975b). Aroclor

1242 was given in single doses of 625, 1,250, or 2,500 mg/kg or five doses of 125 or 250 mg/kg/day. Aroclor 1254 was given in five doses of 75, 150, or 300 mg/kg/day. Treated males were bred to untreated females for the following 10 to 11 weeks. No significant effect of treatment was observed on embryo implantation or lethality with any treatment.

In summary, the only marked genetic effect observed at any level was with the single isomer 4-chlorobiphenyl. Kanechlor 300 and 500 produced cytogenetic effects in different systems but Aroclor 1242 and 1254 did not. Despite the apparent weak mutagenicity of most PCBs in the systems used, the fact that most animals can metabolize many PCB isomers through an arene oxide intermediate indicates that the mutagenic potential of PCBs should not be casually dismissed.

Carcinogenicity

The carcinogenic effects of PCBs have been evaluated in several animal studies. The first evidence of carcinogenic potential in PCBs was reported by Nagasaki, et al. (1972) and in more detail by Ito, et al. (1973). Male dd mice were given Kanachlors 500, 400, and 300 mixed in standard diets at 500, 250, and 100 ppm for 32 weeks. Of 12 mice surviving in the group fed 500 ppm Kanachlor 500, seven (58.3 percent) had grossly observable nodular hyperplasia, with microscopically observable hepatomas in five (41.7 percent). Tumors were not observed in the groups treated with lower doses of Kanechlor 500, in any dose of the other Kanechlors, or in the six control animals. Kimbrough and Linder (1974) treated Bald/cJ mice with Arochlor 1254. Mice were exposed to 300 ppm in the diet for six or 11 months. The mice exposed for six months were fed control diets for the remaining five months, and all the animals were killed and examined at the same time. All the animals surviving 11 months' exposure had enlarged livers and adenofibrosis, while 9/22 (41 percent) were observed to have hepatomas. Of the 24 mice surviving six months' exposure, most showed some changes in liver cell morphology, and a diffuse interstitial fibrosis was observed in about two-thirds of them. One hepatoma (0.3 cm diam.) was observed. The details of the mouse experiments are summarized in Table 10. Kimbrough and Linder (1974) reported subcutaneous abcess formation in some mice and one sweat gland adenoma. Neither Ito, et al. (1973) nor Nagaski, et al. (1972) commented on any pathology other than in the liver.

Studies with rats have been reported by Kimura and Baba (1973), Kimbrough, et al. (1972, 1975), and Ito, et al. (1974). Kimura and Baba (1973) examined the effects of Kanechlor 400 on the livers of Donryu strain rats. Ten male and ten female animals were exposed, in a complex protocol, to amounts of Kanechlor 400 starting at 38.7 ppm in food and increasing to 616 ppm as the animals increased in weight. Total amounts ingested varied from 450 to 1,500 mg over exposure periods of 159 to 560 days. Five control animals of each sex were used. Fatty degeneration was observed in the livers of all experimental animals and two females in the control group. Adenomatous nodules were observed in all of the females which had a cumulative intake of more than 1,200 mg Kanechlor 400. Nodules were seen in none of the males. A number of histopathological findings were noted in spleen, lung, adrenal cortex, and brain, but no neoplastic changes outside the liver were mentioned.

TABLE 10

Evidence for Carcinogenic Effects of PCBs in Mice

Mouse Strain	Sex	No. Treated	No. Surviving	PCB Source	Dietary Level ppm	Average Daily Dose mg/kg/day	Exposure Time (Days)	Liver Nodules: Adenofibrosis	Liver Nodules: Neoplastic Nodules	Liver Nodules: Hepatoma	Liver Nodules: Hepatocellular Carcinoma
dd (Ito, et al. 1973; Nagasaki, et al. 1972)	M	12	12	Kanechlor 500	500	82.5[a]	224	-	7/12		5/12
		12	12	"	250	41.3[a]		-	0/12		0/12
		12	12	"	100	16.5[a]		-	0/12		0/12
				Kanechlor 400	500	82.5			0/12		0/12
				"	250	41.3			0/12		0/12
				"	100	16.5			0/12		0/12
				Kanechlor 300	500	82.5			0/12		0/12
					250	41.3			0/12		0/12
		6	6	Control	100	16.5			0/6		0/6
Balb/cJ (Kimbrough and Linder, 1974)	M	50	22	Aroclor 1254	300	49.8	330	22/22	-	9/22	
		50	24	"	300	49.8[b]	180[c]	0/24	-	1/24	
		100	58	"	-	-	-	0/58	-	0/58	

[a] Calculated using food consumption data from Kimbrough and Linder (1974) for Balb/cJ mice which indicates an average of 165 g/kg/day

[b] Not calculated directly, but assumed to be similar to group exposed 330 days

[c] Maintained on control diet for remaining 150 days of experiment

Ito, et al. (1974) examined the effects of Kanechlors 500, 400, and 300 on male Wistar rats. Animals were exposed to dietary levels of 1,000, 500, and 100 ppm of each preparation for 27 to 52 weeks, then killed and examined for pathological changes. No hepatocellular carcinoma was observed, but cholangiofibrosis (adenofibrosis) was seen at the highest dose of all three agents (Table 11). Nodular hyperplasia was observed in animals treated with all three agents. The highest incidence was observed with Kanechlor 500. Significant changes were not observed in organs other than the liver.

Kimbrough, et al. (1975) exposed Sherman strain rats to Aroclor 1260 at dietary levels of 100 ppm for 21 months. Hepatocellular carcinomas were observed in 26/184 experimental animals but in only one of the controls (1/173). Tumors were observed in several other tissues of both experimental and control groups, but they were of low incidence and frequencies were similar in both groups. In an earlier study, Kimbrough, et al. (1972) fed Aroclor 1254 and 1260 to male and female rats for eight months. Adenofibrosis was observed in animals fed 100 and 500 ppm Aroclor 1254, with the highest incidence in females. Aroclor 1260 was associated with a much lower incidence of adenofibrosis even in animals fed 1,000 ppm. A single bladder tumor was observed in a treated animal but was probably not the result of PCB exposure (Kimbrough, et al. 1975). The details of the experiments with rats are summarized in Table 11.

A report dated November, 1971 described a study made by Industrial Bio-test Laboratories Inc. A brief summary of the report was

TABLE 11

Evidence for Carcinogenic Effects of PCBs in Rats

Strain	Sex	No. Treated	No. Sur-viving	PCB Source	Dietary Level ppm	Average Daily Dose mg/kg/day	Exposure Time (Days)	Liver Nodules		
								Adeno-fibrosis	Neoplastic Nodules	Hepatocellular Carcinoma
Donryue (Kimura and Baba, 1973)	M	10	10	Kanechlor 400	38.5-16	13.5[c]	339[a]	-	0/10	-
	F	10	10	Kanechlor 400	38.5-16	17.5[d]	425[b]	-	6/10	-
	M	5	5	None	-	-	-	-	-	-
	F	5	5	None	-	-	-	-	-	-
Wistar (Ito, et al. 1974)	M	*	13	Kanechlor 500	1,000	49.0[e]	378	4/13	5/13	-
			16	"	500	24.5		0/16	5/16	-
			25	"	100	4.9		0/25	3/25	-
			10	Kanechlor 400	1,000	49.0		2/10	3/10	-
			8	"	500	24.5		0/8	0/8	-
			16	"	100	4.9		0/16	2/16	-
			15	Kanechlor 300	1,000	49.0		2/15	0/15	-
			19	"	500	24.5		0/19	0/19	-
			22	"	100	4.9		0/22	1/22	-
			18	None	0	-	-	0/18	0/18	-

TABLE 11 (cont.)

Strain	Sex	No. Treated	No. Surviving	PCB Source	Dietary Level ppm	Average Daily Dose mg/kg/day	Exposure Time (Days)	Proliferative Changes: Nodular Hyperplasia	Proliferative Changes: Hepatocellular Carcinoma and Adenoma	Proliferative Changes: Combined Hematopoietic and Liver
Fisher 344 rat (NCI, 1978)	M	25	24	Aroclor 1254	0	0	-	0/24	0/24	5/24
			24		25	1.38^e	735	5/24	0/24	2/24
			24		50	2.75^e	735	8/24	1/24	9/24
			24		100	5.5^e	735	12/24	3/24	12/24
	F	25	23		0	0	-	0/23	0/23	4/23
			24		25	1.38^e	735	6/24	$1/24^g$	13/24
			22		50	2.75^e	735	9/22	1/22	8/22
			24		100	5.5^e	735	17/24	2/24	9/24

TABLE 11 (cont.)

Strain	Sex	No. Treated	No. Sur-viving	PCB Source	Dietary Level ppm	Average Daily Dose mg/kg/day	Exposure Time (Days)	Liver Nodules		
								Adeno-fibrosis	Neoplastic Nodules	Hepatocellular Carcinoma
Sherman (Kimbrough, et al 1975)	F	200	184	Aroclor 1260	100	4.9[f]	630	-	144/184	26/184
	F	200	174	None	-	-	630	-	0/173	1/173
Sherman (Kimbrough, et al. 1972)	M	10	10	Aroclor 1260	1,000	71.4	240	2/10	-	-
	F	10	10	"	100	7.2		1/10	-	-
		10	8	"	500	38.2		1/9	-	-
		10	2	"	1,000	72.4		4/7	-	-
	M	10	10	Aroclor 1254	100	6.8		1/10	-	-
		10	10	"	500	36.4		10/10	-	-
	F	10	10	"	100	7.5		7/10	-	-
		10	9	"	500	37.6		9/9	-	-

[a] range 159-530

[b] range 244-560

[c] range of cumulative intake 450-1800 mg

[d] range of cumulative intake 700-1500 mg

[e] Data not provided. Calculated from Kimbrough, et al. 1975, in which Sherman rats showed similar weight gain over the same experimental period.

[f] Time weighted average calculated from Figure 2 in Kimbrough, et al. 1975

[g] Reported as undifferentiated carcinoma of the liver, metastatic

*290 animals total in 10 groups

presented at the National Conference on Polychlorinated Biphenyls (1976), and a more detailed analysis was presented by the U.S. EPA (1976a). One thousand Charles River rats were divided into ten treatment groups. Fifty male and 50 female rats served as a common control group. Each of nine treated groups contained 50 animals of each sex. Groups were fed 1, 10 and 100 ppm of Aroclors 1242, 1254, and 1260, respectively. Treatment was initiated with 4- to 6-week-old animals and continued for a total of 24 months. Five animals of each sex were sacrificed at 3, 6, and 12 months, leaving 35 animals in each group at the beginning of the second year. In addition, mortality was high, leaving only 6 to 21 animals remaining in each treatment/sex subgroup by the end of the experiment. As seen in the previously described studies, the principal effects were observed in the liver. Vacuolar changes and hyperplasia were the major abnormalities originally noted in the treated animals. In addition, chromophobe adenomas of the pituitary were found in eight of nine treated groups but not in the controls. In 1975 the original liver slides were re-evaluated with rather different results. The combined results for animals treated with 100 ppm of all three Aroclors included 11 hepatomas, 5 cholangiohepatomas, and 28 nodular hyperplasias. Hepatocellular carcinomas were not observed.

Recently, a bioassay for the possible carcinogenesis of Aroclor 1254 has been conducted by the National Cancer Institute (1978). In this study, 24 Fischer 344 rats of each sex were orally administered Aroclor 1254 at 25, 50, or 100 ppm for 104 to 105 weeks. Matched controls consisted of 24 untreated rats of each sex. Mortality among the treated males was significantly higher than among the controls and related to dose (P 0.001) but was not different among the females (P 0.05). Interstitial-cell tumors of the testes in males and leukemias of either granulocytic or lymphocytic type were observed frequently in both control and treated animals. Tumors were observed in several other tissues but their presence did not correlate with treatment. Proliferative lesions of the liver were common in treated animals but were not found in controls. The types and frequencies of lesions are detailed in Table 11. They included nodular hyperplasia in all treated groups increasing in frequency with dose, adenomas (one male, three females) and hepatocellular carcinoma (three males, no females). In addition, adenocarcinomas of the stomach, jejunum or cecum of two treated males and two treated females but no controls were observed. Statistical analysis of the frequencies of tumors and proliferative lesions indicated that the combined incidences of leukemia and lymphoma in treated males were significant by one test (Cochran-Armitage test for positive dose-related trend) but not by a more stringent test (Fisher exact test). The tumors of the liver and gastrointestinal tract were not statistically significant; however, the occurrence of nodular hyperplasia appeared to be related to treatment. The study concluded that Aroclor 1254 was not carcinogenic in Fischer 344 rats. However, the high frequency of hepatocellular proliferative lesions was considered to be a result of treatment, and the carcinomas of the gastrointestinal tract also were considered possibly associated with the treatment.

The tumors observed in rodent experiments with PCBs were predominantly adenofibrosis (cholangiofibrosis), neoplastic nodules, and hepatocellular carcinomas. Stewart and Snell (1957) concluded that adenofibrosis cannot be considered to be a pre-malignant lesion, while Reuber (1968) proposed that cholangiofibrosis might be a precursor to cholangiocarcinoma. Neoplastic nodules have been observed before the appearance of carcinomas in several studies with known carcinogens (Kimbrough, et al. 1975). Well-differentiated mouse hepatomas have been shown to be potentially malignant, with a proportion being transplantable and capable of metastasis (Andervant and Dunn, 1952).

Several conclusions can be drawn from the results of the rodent studies. A correlation between degree of chlorination and tumor inducing potential was observed in mice (Ito, et al. 1973) and rats (Ito, et al. 1974) with the most highly chlorinated preparations being most potent. However, Aroclor 1254 was more potent than Aroclor 1260 in rats. Where examined, female rats were found to be more sensitive than males (Kimura and Baba, 1973; Kimbrough, et al. 1972). No comparisons of sex-related effects were made in mice.

It should be noted that none of these studies was a lifetime study. In all cases, animals were treated for fixed times then killed and examined. No lifetime studies with PCBs were found in this survey. Such studies, if available, might indicate more clearly the significance of the potentially preneoplastic lesions induced by PCBs in the studies described here.

Data on the possible carcinogenicity of PCBs in humans are sketchy at this time. The largest group of exposed individuals followed longitudinally are the "Yusho" patients. By late 1973, two of 1,291 patients had died, nine of them with malignant neoplasms (two stomach cancer, one stomach and liver cancer, one liver cancer with cirrhosis, one lung cancer, one lung tumor, one breast cancer, and one malignant lymphoma) (Urabe, 1974; Kuratsune, et al. 1976). The authors did not have sufficient information to make a detailed epidemiological analysis but concluded that 9/22 deaths from cancer may represent an excess of deaths.

Two cases of malignant melanoma were reported in a group of 31 industrial workers exposed "heavily" to Aroclor 1254 in the process of its manufacture. Based on a person-year analysis and the use of the Third National Cancer Survey incidence rates (NCI, 1978), 0.04 malignant melanomas would have been expected making these data significant at the 0.001 level. In addition, one of 41 workers exposed to lower levels of Aroclor 1254 developed a malignant melanoma (Bahn, et al. 1976).

Although these studies involve small numbers of individuals and provide little information about exposure or other relevant factors, they do suggest that human exposure to PCBs may be associated with increased risk of neoplasia.

In addition to the carcinogenic effects observed with PCBs, they have been shown to have a significant effect on the carcinogenic properties of other substances found in the environment. The co-carcinogenic properties of the PCBs result from their ability to induce the mixed function oxidases, particularly in liver, as discussed in the Acute, Subacute, and Chronic Toxicity section. Ito, et al. (1973) observed that dietary levels of 250 ppm Kanechlor 500 markedly promoted hepatocellular carcinoma and nodular hyperplasia in mice exposed to benzene hexachloride at levels of 100 or 250 ppm in the diet. Kanechlor 400 at 10 or 100 ppm in the diet failed to promote cervical carcinoma or progression toward it in mice exposed to 20-methylcholanthrene saturated thread implanted in the cervix and uterus (Uchiyama, et al. 1974). Ito, et al. (1978) observed a pronounced increase in the incidence of preneoplastic, hyperplastic nodules in N-2-fluorenylacetamide treated rats. The animals were fed 1,000 ppm PCB (type not specified) for eight weeks following two weeks exposure to the carcinogen. This increase in preneoplastic lesions over a short period was taken to be a significant indicator of carcinogenic activity. The ability of Aroclor 1254 to initiate (as opposed to promote) tumors in the two-stage mouse skin system was recently examined by DiGiovanni, et al. (1977). Aroclor 1254 proved to be a weak initiator of papillomas when a 100 µg treatment of skin was followed by 32 weeks of treatment with the promotor 12-0-tetradecanoyl-phorbol-13' acetate. When used in combination with the potent initiator dimethylbenzanthracene Aroclor 1254 slightly increased the incidence of papillomas. Aroclor 1254 also failed to promote skin tumors initiated by dimethylbenzanthracene in the same system (100 µg Aroclor 1254 applied twice weekly for 30 weeks) (Berry, et al. 1978).

Kanechlor 500 promoted hepatocellular carcinoma initiated by diethylnitrosamine (DENA) in male Wistar rats (Nishizumi, 1976). Promotion was observed when PCB treatment was begun one week following the end of DENA treatment. The number of tumors was significantly higher in rats treated with DENA and PCB than DENA alone or DENA and phenobarbital, although a promoting effect was observed with the latter drug as well.

Hepatocarcinogenesis initiated by 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) in female Donryu strain rats was promoted by oral administration of PCBs following initiation. Tumor incidences in animals treated with 3'-Me-DAB + PCB, 3'-Me-DAB alone, or PCB alone were 64 percent, 13 percent, and 0 percent, respectively. PCB treatment preceding or simultaneous with 3'-Me-DAB treatment did not produce tumors (Kimura, et al. 1976).

By contrast to the hepatic co-carcinogenic effects of PCBs observed by Kimura, et al. (1976), Nishizumi (1976), and Ito, et al. (1973, 1978), other investigators have observed an inhibition of tumor formation or growth in the presence of PCBs. Makiura, et al. (1974) fed male Sprague-Dawley rats 3'-Me-DAB, 2FAA, DEN, or pair-wise combinations of them for 20 weeks followed by four weeks on a stock diet. Incidence of hepatocellular carcinoma ranged from 65.2 to 92.3 percent, and nodular hyperplasia reached 100 percent in animals fed pairs of carcinogens. The addition of 50 ppm Kanechlor 500 to the diet resulted in a large decrease in the tumor incidence and liver weight as compared to carcinogen treatment without PCBs. PCBs alone induced no tumors or hyperplastic nodules but did result in an increased liver weight. The principal difference between this study and those of Ito, et al. (1978), Nishizumi (1976), and Kimura, et al. (1976) using the same chemicals is that PCB exposure was delayed until after the initiating treatment in the latter studies. This suggests that the induction of mixed function oxidases by PCB at the time of carcinogen treatment results primarily in the inactivation of the chemicals and that the promoting effects observed with sequential exposure result from some other mechanism. The co-carcinogenesis of PCBs with simultaneous exposure to BHC may reflect a difference in the liver metabolism of this compound.

In rainbow trout, Salmo gairdnerii, 100 ppm Aroclor 1254 added to the diet reduced the size and frequencies of liver tumors induced by 6 ppm aflatoxin B_1 after a one year exposure (Hendricks, et al. 1977).

In addition to the inhibition of tumor induction by some chemicals, PCBs were also shown to inhibit the growth of experimental tumors in rats. Sprague-Dawley rats were inoculated with Walker 256 Carcinosarcoma cells and the effects of PCBs determined. Both dietary (Kerkvliet and Kimeldorf, 1977a) and injected (Kerkvliet and Kimeldorf, 1977b) Aroclor 1254 reduced the size of solid tumors and increased animal life span. Total dietary PCB intake of 1,100 to 2,000 mg/kg over a 40-day period reduced tumor weight to 60 to 40 percent of control in both male and female rats. Aroclor 1254 injected intraperitoneally reduced the efficiency of tumor takes when 10^3 tumor cells were injected from 81.3 in control to 50.0 percent in animals receiving 200 mg/kg/day. Mean tumor sizes were reduced and lifespans increased by PCBs in animals inoculated with 10^7 tumor cells. Administration of PCBs for five days preceding tumor inoculation or the first five days after inoculation was more effective than administration between days 5 and 10.

CRITERION FORMULATION

Existing Guidelines and Standards

The Toxic Substances Control Act (TSCA) (P.L. 94-469) was signed into law October 11, 1976. Provisions in section 6(e) of the law specifically regulate the manufacture, sale, distribution, and disposal of PCBs. Manufacture, sale, or distribution of PCBs was restricted to sealed systems as of October 11, 1977. Manufacture was banned as of January 1, 1979 and all processing and distribution in commerce ceased July 1, 1979. Allowance for certain exemptions is provided in the law. The proposed rules to implement the terms of section 6(e) of TSCA were released June 7, 1978 (43 FR 24802). Proposed rules on the disposal of PCBs were released February 17, 1978 (43 FR 7150). The U.S. Environmental Protection Agency has proposed a water quality criterion for the protection of freshwater and marine life of 0.001 µg/l (U.S. EPA, 1976b). The Food and Drug Administration established tolerance levels in foods in 1973 (38 FR 18096) and proposed new tolerance levels further restricting levels in 1977 (42 FR 17487). Both the current allowed levels and the proposed levels were presented in Table 3.

The occupational exposure limits adopted in 1968 are based on the recommendations of the American Conference of Governmental Industrial Hygienists (ACGIH, 1968). They set the time-weighted average eight-hour exposure limits to 1.0 mg/m^3 for mixtures containing 42 percent chlorine and 0.5 mg/m^3 for mixtures containing 54 percent chlorine. The newly recommended standard proposed by NIOSH (1977) is 1.0 µg/m^3 air TWA over a 10-hour day and 40-hour work week.

Current Levels of Exposure

Human exposure to PCBs in the United States has been broad. Several studies of tissue and plasma levels of PCBs have detected them in a high percentage of randomly chosen subjects. Yobs (1972) detected PCBs in 31.1 percent of 637 human adipose tissue. The National Human Monitoring Program for Pesticides in fiscal years 1973 and 1974 found PCBs in 35.1 and 40.3 percent of adipose tissues tested (Kutz and Strassman, 1976). Table 12 indicates the distribution of PCB concentrations in the population. A study of Canadian human adipose tissue PCB levels found 1 ppm or more in 30 percent of 172 samples (Grant, et al. 1976). The eastern provinces, particularly Ontario, had the highest incidences. Average adipose tissue PCB levels were just below 1 mg/kg (ppm) with males having slightly higher accumulations than females. The same study found human breast milk to contain about 1 mg/kg on a fat basis. PCBs were detected in 8 of 40 samples of breast milk in Colorado at levels between 40 and 100 ppb (whole milk). The Japanese study described earlier found average levels in 400 milk samples of about 30 ppb (Yakushiji, et al. 1977). PCB levels in plasma in U.S. populations were detected in 43 percent of 723 samples. Levels in positive samples ranged from 1.5 to 29 ppb with a mean around 2 to 3 ppb. White populations had higher levels than black populations (Finklea, et al. 1972).

As discussed in the section on exposure, the median water levels of PCBs are around 0.1 to 0.3 µg/l in positive samples with 0 to 20 percent of samples being positive around the U.S. (Dennis, 1976). Average PCB intake in food was estimated in the mid-1970's

TABLE 12

Levels of Polychlorinated Biphenyls in Human Adipose Tissue*

Data Source	Sample Size	Percent Nondetected	Percent 1 ppm	Percent 1-2 ppm	Percent 2 ppm
Yobs, 1972	688	34.2	33.3	27.3	5.2
FY 1973 Survey	1,277	24.5	40.2	29.6	5.5
FY 1974 Survey	1,047	9.1	50.6	35.4	4.9

*Source: Kutz and Strassman, 1976

to be about 9 µg/day with fish being the major dietary source. Ambient air concentrations are around 100 ng/m^3 (Kutz and Yang, 1976).

Special Groups at Risk

The preceding discussion of human exposure makes clear the fact that a high percentage of the U.S. population has been and is exposed to low levels of PCBs in food, water, and air. Those groups at particular risk for PCB exposure include industrial workers exposed in the workplace, individuals consuming large amounts of contaminated fish, such as sport fisherman (42 FR 17487), and nursing infants who, per kg body weight, may accumulate significant body burdens from the levels in human breast milk. With the cessation of manufacture of PCBs by Monsanto in 1977 and the great decline in its use which should result from the implementation of section 6(e) of TSCA, industrial exposure should decline substantially. Since many PCB-containing sealed systems can be expected to remain in service for many years, continuing vigilance will be necessary to minimize accidental pollution of waterways or air and to prevent further occupational exposure.

Basis and Derivation of Criterion

In arriving at a criterion for PCB levels in ambient waters several factors must be taken into account. First, PCBs are highly persistent in the environment and accumulate to a high degree in food webs. As discussed in the section Ingestion from Foods, an average bioaccumulation factor for PCBs in all freshwater fish and shellfish of 31,200 has been determined. As a consequence, PCBs leave the environment very slowly once they have entered it. Not only do PCBs persist and accumulate in the environment but in man as well. The current environmental levels are not producing obvious acute ill health in the general population. However, several animal studies report that PCBs produce a carcinogenic response and that they may enhance the carcinogenic activities of other substances.

Although other adverse effects of PCB exposure could be used as a basis for formulating a criterion, carcinogenicity will be used for a variety of reasons. The most extensive chronic studies with PCBs have identified carcinogenicity as the major end point. Although no carcinogenicity studies have been extended to more than one generation and firm data exist only for the female rat, a credible carcinogenic response to PCBs has been demonstrated and cannot be ignored. Kimbrough, et al. (1972) observed an incidence of hepatocellular carcinoma of 26/184 in treated rats compared to 1/173 in controls. The National Cancer Institute (NCI) bioassay observed a lower percentage of hepatocellular carcinoma at a similar dose level which was statistically not significant because the number of animals was low. In addition, a number of nonmalignant proliferative processes observed in liver at high frequencies in the PCB-treated animals in these studies were also observed in both rats and mice in other studies (Ito, et al. 1973, 1974; Kimura and Baba 1973; Kimbrough, et al. 1972; Kimbrough and Linder, 1974). PCBs were classified as carcinogenic by the International Agency for Research on Cancer (IARC, 1974). Evidence from human populations suggests but does not confirm an increase in cancer frequency due to PCB exposure (Kuratsune, et al. 1976; Bahn, 1976). Finally, a theoretical basis exists for the quantitative extrapolation of carcinogenic effects in treated animals to human populations. Various models, such as the one used below, can provide quantitative risk estimates based on animal data and certain assumptions about the induction of neoplasia (e.g. one-hit or multi-hit induction). No basis exists for extrapolation with mathematical models from animals to man for many other kinds of biological effects.

Although the criterion established below is based on animal carcinogenicity data, it should also be noted that other adverse effects have been observed in mammals at levels below the dose which produces tumors in rats. The carcinogenic effect was observed in rats consuming an average of 4.9 mg/kg/day. Dietary levels at 2.5 ppm produced adverse reproductive effects in Rhesus monkeys (Allen and Barsotti, 1976). If a food intake of 350 g/day is assumed, the PCB dose is 146 µg/kg/day in 6 kg animals. At this time no data are available to indicate the minimal level in the diet at which PCBs produce toxic effects in Rhesus monkeys.

In mink, ingestion of as little as 61 mg of Aroclor 1254 over nine months or 90 mg of Aroclor over four months resulted in sharply reduced reproduction (Aulerich and Ringer, 1977). Assuming a weight of 1 kg for adult mink and a food intake of 150 g/day, the PCB dose at 2 ppm was about 300 µg/kg/day, which is similar to the level producing reproductive toxicity in monkeys.

These data can be used in one approach to developing an ambient water quality criterion. If 300 µg/kg/day is taken as the lowest-observable-effect-level (LOEL), then an Acceptable Daily

Intake (ADI) can be calculated for a 70 kg man using an uncertainty factor of 100:

$$\frac{300 \times 70}{100} = 210\ \mu g/day$$

Assuming that exposure to PCBs is based on the consumption of 2 liters of drinking water, 6.5 g (0.0065 kg) of fish and shellfish, and a bioconcentration factor of 31,200; then the following calculation can be made:

$$X\ [(2\ l) + (0.0065 \times 31,200)] = 210\ \mu g$$

$$X = 1.03\ \mu g/l$$

As will be seen later, the carcinogenicity criterion is lower and presumably more cautionary.

An assessment of carcinogenic risk will be made by extrapolation from animal data using a linearized multistage (non-threshold) model. The extrapolation used takes into account the bioaccumulation of PCBs in fish and shellfish. It is assumed that an average of 2 l/day of water are consumed along with 6.5 g of fish taken from that water source. Exposures from other food sources, air, or occupational exposure are not included in the criterion level derived by this model.

Among the studies reviewed in this document, only one appears suitable for use in the cancer risk assessment. None of the mouse studies involved feeding for most or all of a lifetime and are therefore unsuitable. Of the rat studies, the only one involving long term exposure and adequate numbers of animals is the study of Sherman rats by Kimbrough, et al. (1975).

This study has some drawbacks in that it lacks any evidence of a dose-response (due to the use of only one dose level); it tests only one sex of the species, and only one commercial mixture of PCBs. Yet the experimental design is a good one in many ways: the treatment was given over a long portion of the life span; there was an appropriate route (food) and distribution of exposure (uniform dose over time); the authors provided good documentation of the actual intake dose; a sufficiently large number of experimental and control animals were used to detect a statistically significant increase in tumors; and there was a thorough and well documented description of the pathology (hepatocellular carcinoma). The NCI study (1978) was the only other study involving a long-term exposure and was suggestive of a carcinogenic effect; however, the lack of an adequate number of animals renders it unsuitable as a study upon which to base an estimate of carcinogenic risk.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." PCBs are suspected of being human carcinogens. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of PCBs in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentration of PCBs corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g fish and shellfish. (2)	0.0079 ng/l	0.079 ng/l	0.79 ng/l
Consumption of fish and shellfish only.	0.0079 ng/l	0.079 ng/l	0.79 ng/l

(1) Calculated by applying a linearized multistage model as discussed in the Human Health Appendices to the October 1980 Federal Register notice which announced the availability of this document. Appropriate bioassay data used in the calculation are presented in the Appendix. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Approximately 99 percent of the PCB exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 31,200-fold. The remaining 1 percent of PCB exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of PCBs, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding PCBs concentrations, and (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding PCB concentrations. Although total exposure information for PCBs is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into ambient water quality criteria formulation until additional analysis can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

These criteria are exceedingly low. Although sharp restriction of open PCB use in 1970 resulted in notable declines in water PCB levels in the next several years (Dennis, 1976), the residual levels remaining are still two to three orders of magnitude above the criterion indicated by this extrapolation. The major source of PCBs in water today is probably not new effluents from industrial or domestic sources, but the PCB-containing sludges underlying waterways which typically contain 100- to 1,000-fold higher concentrations than the water itself (Dennis, 1976). Efforts to reduce water levels significantly by eliminating current pollution sources will probably have little effect on average water PCB concentrations.

The very low limits suggested by this risk estimate are due in large part to the very large bioaccumulation factor in fish (31,200). This figure is an average for a wide variety of salt-water and freshwater organisms (see Ingestion from Food section).

As possible strategies to reduce human exposures to PCBs are considered, the relative contributions of ingested water and fish should be kept in mind. At the assumed consumption rate of 2 liters of drinking water and 6.5 g of fish/day, 99 percent of the dietary PCBs will be obtained from fish. Strategies which focus separately on the reduction of PCB levels in water and fish for human consumption might be more practical and productive than a single standard for water which takes bioaccumulation in fish into account.

A final comment about the risk level derived from this study is that it is based on animal data in which a dose-response relationship was not demonstrated. The weight of evidence indicates that PCBs are carcinogenic in rodents. However, the carcinogenic activities of these compounds are not great. An acceptable noncarcinogenic level could be established with greater certainty if better quantitative data on carcinogenicity were available. Studies with larger numbers of animals designed to measure relatively small effects are needed. Also, the rat appears to be much less sensitive to the acute and subacute effects of PCBs than man or nonhuman primates. Further investigation of the effects of PCBs in Rhesus monkeys, particularly with reference to the gastric lesions produced, would be useful.

REFERENCES

Abe, S., et al. 1975. Polychlorinated biphenyls residues in plasma of Yusho children born to mothers who had consumed oil contaminated by PCB. Fukuoka Acta Med. 66: 605. (Jap.)

Albro, P.W. and L. Fishbein. 1972. Intestinal absorption of polychlorinated biphenyls in rats. Bull. Environ. Contam. Toxicol. 8: 26.

Allen, J.R. 1975. Response of the non-human primate to polychlorinated biphenyl exposure. Fed. Proc. 34: 1675.

Allen, J.R. and L.J. Abrahamson. 1973. Morphological and biochemical changes in the liver of rats fed polychlorinated biphenyls. Arch. Environ. Contam. Toxicol. 1: 265.

Allen, J.R. and D.A. Barsotti. 1976. The effects of transplacental and mammary movement of the PCBs on infant Rhesus monkeys. Toxicology. 6: 331.

Allen, J.R. and D.H. Norback. 1973. Polychlorinated biphenyl- and triphenyl-induced gastric mucosal hyperplasia in primates. Science. 179: 498.

Allen, J.R. and D.H. Norback. 1976. Pathobiological Responses of Primates to Polychlorinated Biphenyl Exposure. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, Chicago, Illinois. EPA 560/6-75-004. Off. Tox. Subst., U.S. Environ. Prot. Agency, Washington, D.C. p. 43.

Allen, J.R. and D.H. Norback. 1977. Carcinogenic Potential of the Polychlorinated Biphenyls. In: H.H. Hiatt, et al. (eds.), Origins of Human Cancer. Cold Spring Harbor Conf. Cell Prolif. Cold Spring Harbor Lab., Cold Spring Harbor, New York. 4: 173.

Allen, J.R., et al. 1974a. Tissue modifications in monkeys as related to absorption distribution and excretion of polychlorinated biphenyls. Arch. Environ. Contam. 2: 86.

Allen, J.R., et al. 1974b. Residual effects of short-term, low-level exposure of non-human primates to polychlorinated biphenyls. Toxicol. Appl. Pharmacol. 30: 440.

Allen, J.R., et al. 1975. Responses of rats and non-human primates to 2,5,2',5'-tetrachlorobiphenyl. Environ. Res. 9: 265.

Alvares, A.P. and A. Kappas. 1975. Induction of aryl hydrocarbon hydroxylase by polychlorinated biphenyls in the foeto-placental unit and neonatal livers during lactation. FEBS Lett. 50: 172.

Alvares, A.P., et al. 1973. Polychlorinated biphenyls: A new type of inducer of cytochrome P-448 in the liver. Proc. Natl. Acad. Sci. 70: 1321.

Alvares, A.P., et al. 1977. Alterations in drug metabolism in workers exposed to polychlorinated biphenyls. Clin. Pharmacol. Ther. 22: 140.

American Conference of Governmental Industrial Hygienists. 1968. Threshold limit values for 1968 - recommended and intended values, adopted at 30th Annu. Meet. St. Louis, May 13.

Anderson, M.W., et al. 1977. The construction of a pharmacokinetic model for the disposition of polychlorinated biphenyls in the rat. Clin. Pharmacol. Ther. 22: 765.

Andervant, H.B. and T.B. Dunn. 1952. Transplantation of spontaneous and induced hepatomas in inbred mice. Jour. Natl. Cancer Inst. 13: 455.

Aulerich, R.J. and R.K. Ringer. 1977. Current status of PCB toxicity, including reproduction to mink. Arch. Environ. Contam. Toxicol. 6: 279.

Aulerich, R.J., et al. 1971. Effects of feeding coho salmon and other Great Lakes fish on mink reproduction. Can. Jour. Zool. 49: 611.

Aulerich, R.J., et al. 1973. Reproductive failure and mortality in mink fed on Great Lakes fish. Jour. Reprod. Fert. (Suppl.) 19: 365.

Bahn, A.K., et al. 1976. Melanoma after exposure to PCBs. New England Jour. Med. 295: 450.

Barsotti, D.A. and J.R. Allen. 1975. Effects of polychlorinated biphenyls on reproduction in the primate. Fed. Proc. 34: 338.

Barsotti, D.A., et al. 1976. Reproductive dysfunction in Rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248). Food Cosmet. Toxicol. 14: 99.

Bastomsky, C.H. 1974. Effects of a polychlorinated biphenyl mixture (Aroclor 1254) and DDT on biliary thyroxin excretion in rats. Endocrinology. 94: 1150.

Bell, M. 1976. Ultrastructural Features of Gastric Mucosa and Sebaceous Glands after Ingestion of Aroclor 1242 by Rhesus Monkeys. In: Natl. Conf. Polychlor. Biphenyls, Nov. 19-21, Chicago, Illinois. EPA 560/6-75-004. Off. Tox. Subst., U.S. Environ. Prot. Agency, Washington, D.C. p. 350.

Benthe, H.F., et al. 1972. Absorption and distribution of polychlorinated biphenyls (PCB) after inhalatory application. Arch. Toxicol. 29: 85.

Berry, D.L., et al. 1978. Lack of tumor-promoting ability of certain environmental chemicals in a two-stage mouse skin tumorigenesis assay. Res. Commun. Chem. Pathol. Pharmacol. 20: 101.

Bickers, D.R. 1976. Tissue profiles of carcinogen metabolism following skin application of chemical inducers. Jour. Invest. Dermatol. 66: 279.

Bickers, D.R., et al. 1972. Polychlorinated biphenyls. Comparative effects of high and low chlorine containing Aroclors on hepatic mixed function oxidase. Res. Commun. Chem. Pathol. Pharmacol. 3: 505.

Bickers, D.R., et al. 1975. Microscope immersion oils: Effects of skin application on cutaneous and hepatic drug-metabolizing enzymes. Biochem. Pharmacol. 24: 779.

Billings, W.N., et al. 1978. Movement of PCB from a contaminated reservoir into a drinking water supply. Bull. Environ. Contam. Toxicol. 19: 244.

Bitman, J. and H.C. Cecil. 1970. Estrogenic activity of DDT analogs and polychlorinated biphenyls. Jour. Agric. Food Chem. 18: 1108.

Bowman, R.E., et al. 1978. Correlation of PCB body burden with behavioral toxicology in monkeys. Pharmacol. Biochem. Behav. 9: 49.

Bruckner, J.V., et al. 1973. Biological responses of the rat to polychlorinated biphenyls. Toxicol. Appl. Pharmacol. 24: 434.

Bruckner, J.V., et al. 1974. Effect of prolonged ingestion of polychlorinated biphenyls on the rat. Food Cosmet. Toxicol. 12: 323.

Bruckner, J.V., et al. 1977. The influence of ingestion of environmentally encountered levels of a commercial polychlorinated biphenyl mixture (Aroclor 1254) on drug metabolism in the rat. Jour. Pharmacol. Exp. Ther. 202: 22.

Burse, V.W., et al. 1974. Polychlorinated biphenyls. Storage, distribution, excretion, and recovery: Liver morphology after prolonged dietary ingestion. Arch. Environ. Health. 29: 301.

Carey, A.E. and J.A. Gowan. 1976. PCBs in Agricultural and Urban Soil. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, 1975, Chicago, Illinois. EPA 560/6-75-004. Off. Tox. Subst., U.S. Environ. Prot. Agency, Washington, D.C.

Chen, P.R. and H.B. Matthews. 1974. Metabolism and excretion of 2,4,5,2',5'-pentachlorobiphenyl (PCB) in the male rat. Toxicol. Appl. Pharmacol. 29: 88.

Collins, W.T., et al. 1977. Effect of polychlorinated biphenyl (PCB) on the thyroid gland of rats. Ultrastructural and biochemical investigations. Am. Jour. Pathol. 89: 119.

Crump-Wiesner, H.J., et al. 1974. Pesticides in water. A study of the distribution of polychlorinated biphenyls in the aquatic environment. Pestic. Monitor. Jour. 8: 157.

Curley, A., et al. 1973. Polychlorinated biphenyls: Evidence of transplacental passage in the Sherman rat. Food. Cosmet. Toxicol. 11: 471.

Daly, J.W., et al. 1972. Arene oxides and the NIH shift. The metabolism, toxicity and carcinogenicity of aromatic compounds. Experientia. 28: 1129.

Dennis, D.S. 1976. Polychlorinated Biphenyls in the Surface Waters and Bottom Sediments of the Major Drainage Basins of the United States. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, Chicago, Illinois. EPA 560/6-75-004. Off. Tox. Subst., U.S. Environ. Prot. Agency, Washington, D.C. p. 183.

DiGiovanni, J., et al. 1977. Tumor-initiating ability of 2,3,4,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and Aroclor 1254 in the two-stage system of mouse skin carcinogenesis. Bull. Environ. Contam. Toxicol. 18: 552.

Dikshith, T.S.S., et al. 1975. Effects of a polychlorinated biphenyl (Aroclor 1254) on rat testis. Exp. Mol. Pathol. 22: 376.

Drinker, C.K., et al. 1937. The problem of possible systemic effects from certain chlorinated hydrocarbons. Jour. Ind. Hyg. Toxicol. 19: 283.

Duke, T.W., et al. 1970. A polychlorinated biphenyl (Aroclor® 1254) in the water, sediment and biota of Escambia Bay, Florida. Bull. Environ. Contam. Toxicol. 5: 171.

Ecobichon, D.J. 1975. The influence of polychlorinated biphenyl compounds on the hepatic function in the rat. Environ. Sci. Res. 7: 20.

Ecobichon, D.J. and A.M. Comeau. 1975. Isomerically pure chlorobiphenyl congeners and hepatic function in the rat: Influence of position and degree of chlorination. Toxicol. Appl. Pharmacol. 33: 94.

Elkins, H.B. 1959. The Chemistry of Industrial Toxicology. John Wiley and Sons, New York.

Finklea, J., et al. 1972. Polychlorinated biphenyl residues in human plasma expose a major urban pollution problem. Am. Jour. Pub. Health. 62: 645.

Fishbein, L. 1972. Chromatographic and biological aspects of polychlorinated biphenyls. Jour. Chromatogr. 68: 345.

Fishbein, L. 1974. Toxicity of chlorinated biphenyls. Ann. Rev. Pharmacol. 14: 139.

Gardener, A.M., et al. 1973. Polychlorinated biphenyls: Hydroxylated urinary metabolites of 2,2',5,5'-tetrachlorobiphenyl identified in rabbits. Biochem. Biophys. Res. Commun. 55: 1377.

Goldstein, J.A., et al. 1977. Separation of pure polychlorinated biphenyl isomers into two types of inducers on the basis of induction of cytochrome P-450 or P-448. Chem. Biol. Interact. 17: 69.

Goldstein, J.A., et al. 1978. 2,3,7,8-Tetrachlorodibenzofuran in a commercially available 99 percent pure polychlorinated biphenyl isomer identified as the inducer of hepatic cytochrome P-448 and aryl hydrocarbon hydroxylase in the rat. Drug Metab. Dispos. 6: 258.

Grant, D.L., et al. 1976. PCB Residues in Human Adipose Tissue and Milk. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, Chicago, Illinois. EPA 560/75-004. Off. Tox. Subst., U.S. Environ. Prot. Agency, Washington, D.C. p. 144.

Green, S., et al. 1975a. Lack of cytogenetic effects in bone marrow and spermatogonial cells in rats treated with polychlorinated biphenyls Aroclors [illegible]42 and 1254. Bull. Environ. Contam. Toxicol. 13: 14.

Green, S., et al. 1975b. Lack of dominant lethality in rats treated with polychlorinated biphenyls (Aroclors 1242 and 1254). Food Cosmet. Toxicol. 13: 507.

Grover, P.L. and P. Sims. 1970. Interaction of k-region epoxides of phenanthrene and dibenz(a,h)anthracene with nucleic acids and histones. Biochem. Pharmacol. 19: 2251.

Grover, P.L., et al. 1975. The carcinogenicity of polycyclic hydrocarbon epoxides in newborn mice. Br. Jour. Cancer. 31: 182.

Haile, C.L., et al. 1975. Chlorinated hydrocarbons in the Lake Ontario ecosystem (IFYGL). U.S. EPA Ecological Research Series, EPA 660/3-75-022, Corvallis, Oregon.

Hara, I., et al. 1974. Follow-up study of condenser factory after use of PCB discontinued (Part I). Jap. Jour. Ind. Health. 16: 365.

Hara, I., et al. 1975. Follow-up study of condenser factory after use of PCB discontinued (Part III). Jap. Jour. Ind. Health. 17: 371.

Hasegawa, H., et al. 1972. Report on Survey of Work Area Environment where PCB is Handled and the Health of Workers Handling PCB. _In_: Special Research Report on Prevention of Environmental Pollution by PCB-like Substances. Res. Coor. Bur. Sci. Technol. Agency, Japan. Cited in National Institute of Occupational Safety and Health. 1977. Criteria for a recommended standard... occupational exposure to polychlorinated biphenyls. DHEW (NIOSH) Publ. No. 77-225, p. 141.

Hass, J.R., et al. 1977. Metabolism of 4-chlorobiphenyl and 4,4'-dichlorobiphenyl in the rat: Qualitative and quantitative aspects. Jour. Agric. Food Chem. 25: 1330.

Heddle, J.A. and W.R. Bruce. 1977. Comparison of Tests for Mutagenicity or Carcinogenicity using Assays for Sperm Abnormalities, Formation of Micronuclei and Mutations in _Salmonella_. _In_: H.H. Hiatt, et al. (eds.), Origins of Human Cancer. Cold Spring Harbor Conf. Cell Prolif. Cold Spring Harbor Lab., Cold Spring Harbor, New York. 4: 1549.

Hendricks, J.D., et al. 1977. Inhibitory effect of a polychlorinated biphenyl (Aroclor 1254) on aflatoxin B_1 carcinogenesis in rainbow trout (_Salmo gaidneri_). Jour. Natl. Cancer Inst. 59: 1545.

Hirayama, C., et al. 1974. Hypobilirubinemia in patients with polychlorinated biphenyls poisoning. Clin. Chim. Acta. 55: 97.

Hodge, H.C. and J.H. Sterner. 1949. Tabulation of toxicity classes. Am. Ind. Hyg. Assoc. Q. 10: 93.

Hsu, I.C., et al. 1975a. Metabolic fate of ^{3}H 2,5,2',5'-tetrachlorobiphenyl in infant nonhuman primates. Bull. Environ. Contam. Toxicol. 14: 233.

Hsu, I.C., et al. 1975b. Urinary metabolites of 2,5,2',5'-tetrachlorobiphenyl in the non-human primate. Proc. Soc. Exp. Biol. Med. 150: 185.

Huberman, E., et al. 1972. Transformation of hamster embryo cells by epoxides and other derivatives of polycyclic hydrocarbons. Cancer Res. 32: 1391.

Hutzinger, O., et al. 1972. Polychlorinated biphenyls: Metabolic behavior of pure isomers in pigeons, rats and brook trout. Science. 178: 312.

International Agency for Research on Cancer. 1974. Monographs on the evaluation of the carcinogenic risk of chemicals to man: Some anti-thyroid and related substances, nitrofurans and industrial chemicals, Vol. 7. Lyon, France.

Ito, N., et al. 1973. Histopathologic studies on liver tumorigenesis induced in mice by technical polychlorinated biphenyls and its promoting effect on liver tumors induced by benzene hexachloride. Jour. Natl. Cancer Inst. 51: 1637.

Ito, N., et al. 1974. Histopathological studies on liver tumorigenesis in rats treated with polychlorinated biphenyls. Gann. 65: 545.

Ito, N., et al. 1978. Enhancing effects of chemicals on production of hyperplastic liver nodules induced by N-2 fluorenyl-acetamide in hepatectomized rats. Gann. 69: 143.

Jelinek, C.F. and P.E. Corneliussen. 1976. Levels of PCBs in the U.S. Food Supply. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, Chicago, Illinois. EPA 560/6-75-004. Off. Tox. Subst., U.S. Environ. Prot. Agency, Washington, D.C.

Johnstone, G.J., et al. 1974. The influence of pure polychlorinated biphenyl compounds on hepatic function in the rat. Toxicol. Appl. Pharmacol. 28: 66.

Jones, J.W. and H.S. Alden. 1936. An acneform dermatergosis. Arch. Dermat. Syphilol. 33: 1022.

Kerkvliet, N.I. and D.J. Kimeldorf. 1977a. Inhibition of tumor growth in rats by feeding a polychlorinated biphenyl, Aroclor 1254. Bull. Environ. Contam. Toxicol. 18: 243.

Kerkvliet, N.I. and D.J. Kimeldorf. 1977b. Antitumor activity of a polychlorinated biphenyl mixture, Aroclor 1254, in rats inoculated with Walker 256 carcinoma cells. Jour. Natl. Cancer Inst. 59: 951.

Kihlstrom, J.E., et al. 1975. Sexual functions of mice neonatally exposed to DDT or PCB. Environ. Physiol. Biochem. 5: 54.

Kimbrough, R.D. 1974. The toxicity of polychlorinated polycyclic compounds and related chemicals. CRC Crit. Rev. Toxicol. 2: 445.

Kimbrough, R.D. and R.E. Linder. 1974. Induction of adenofibrosis and hepatomas in the liver of Balb/cJ mice by polychlorinated biphenyls (Aroclor 1254). Jour. Natl. Cancer Inst. 53: 547.

Kimbrough, R.D., et al. 1972. Morphological changes in livers of rats fed polychlorinated biphenyls. Arch. Environ. Health. 25: 354.

Kimbrough, R.D., et al. 1975. Induction of liver tumors in Sherman strain female rats by polychlorinated biphenyl Aroclor 1260. Jour. Natl. Cancer Inst. 55: 1453.

Kimbrough, R., et al. 1978. Animal toxicity. Environ. Health Perspect. 24: 173.

Kimura, N.T. and T. Baba. 1973. Neoplastic changes in the rat liver induced by polychlorinated biphenyl. Gann. 64: 105.

Kimura, N.T., et al. 1976. Polychlorinated biphenyl(s) as a promoter in experimental hepatocarcinogenesis. Z. Krebsforsch Klin. Onkol. 87: 257.

Koda, H. and Y. Masuda. 1975. Relation between PCB level in blood and clinical symptoms of Yusho patients. Fukuoka Acta. Med. 66 624. (Jap.)

Koller, L.D. and J.G. Zinkl. 1973. Pathology of polychlorinated biphenyls in rabbits. Am. Jour. Pathol. 70: 363.

Kuratsune, M. 1972. An abstract of results of laboratory examinations of patients with Yusho and animal experiments. Environ. Health Perspect. 1: 129.

Kuratsune, M., et al. 1972. Epidemiologic study on Yusho, a poisoning caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyls. Environ. Health Perspect. 1: 119.

Kuratsune, M., et al. 1976. Some of the Recent Findings Concerning Yusho. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, 1975, Chicago, Illinois. EPA 560/6-75-004. U.S. Environ. Prot. Agency, Washington, D.C. p. 14.

Kutz, F.W. and S.C. Strassman. 1976. Residues of Polychlorinated Biphenyls in the General Population of the United States. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, 1975, Chicago, Illinois. EPA 560/75-004. U.S. Environ. Prot. Agency, Washington, D.C. p. 139.

Kutz, F.W. and H.S.C. Yang. 1976. A Note on Polychlorinated Biphenyls in Air. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, 1975, Chicago, Illinois. EPA 560/6-75-004. Off. Tox. Subst., U.S. Environ. Prot. Agency, Washington, D.C. p. 182.

LaRocca, P.T. and G.P. Carlson. 1975. The inhibitory activity of polychlorinated biphenyls on ATPase activity. Fed. Proc. 34: 246.

Levy, B.S.B., et al. 1977. Health hazard evaluation determination. Rep. No. 76-52-386. Westinghouse Electric Corp. Bloomington, Indiana. U.S. Dept. Health Edu. Welfare Center for Disease Control, Cincinnati.

Linder, R.E., et al. 1974. The effect of PCB on rat reproduction. Food Cosmet. Toxicol. 12: 63.

Litterst, C.L. and E.J. VanLoon. 1972. Enzyme induction by polychlorinated biphenyls relative to known inducing agents. Proc. Soc. Exp. Biol. Med. 141: 765.

Litterst, C.L. and E.J. VanLoon. 1974. Time-course of induction of microsomal enzymes following treatment with polychlorinated biphenyl. Bull. Environ. Contam. Toxicol. 11: 206.

Litterst, C.L., et al. 1972. Effect of polychlorinated biphenyls on hepatic microsomal enzymes in the rat. Toxicol. Appl. Pharmacol. 23: 112.

Lutz, R.J., et al. 1977. A preliminary pharmacokinetic model for several chlorinated biphenyls in the rat. Drug Metab. Dispos. 5: 386.

Makiura, S., et al. 1974. Inhibitory effect of polychlorinated biphenyls on liver tumorigenesis in rats treated with 3'-methyl-4-dimethylaminobenzene, N-2-fluorenylacetamide and diethylnitrosamine. Jour. Natl. Cancer Inst. 53: 1253.

Masuda, Y., et al. 1974. Polychlorinated biphenyls in Yusho patients and ordinary persons. Fukuoka Acta. Med. 65: 17. (Jap.)

Masuda, Y., et al. 1978. Transfer of polychlorinated biphenyls to the foetuses and offspring of mice. Food Cosmet. Toxicol. 16: 33.

Matthews, H.B. and M.W. Anderson. 1975a. The distribution and excretion of 2,4,5,2',5'-pentachlorobiphenyl in the rat. Drug Metab. Dispos. 3: 211.

Matthews, H.B. and M.W. Anderson. 1975b. Effect of chlorination on the distribution and excretion of polychlorinated biphenyls. Drug Metab. Dispos. 3: 371.

Matthews, H., et al. 1978. Metabolism and biochemical toxicity of PCBs and PBBs. Environ. Health Perspect. 24: 147.

McCloskey, F.X., et al. 1978. Polychlorinated biphenyl exposure - Indiana. Morbid. Mortal. Weekly Rep. 27: 99.

McNulty, W.P. 1976. Primate Study. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, Chicago, Illinois. EPA 560/6-75-004. Off. Tox. Subst., U.S. Environ. Prot. Agency, Washington, D.C. p. 347.

Meigs, J.W., et al. 1954. Chloracne from an unusual exposure to Arochlor. Jour. Am. Med. Assoc. 154: 1417.

Miller, J.W. 1944. Pathologic changes in animals exposed to a commercial chlorinated diphenyl. Pub. Health Rep. 59: 1085.

Mizunoya, Y., et al. 1974. Effects of polychlorinated biphenyls on fetuses and offsprings in rats. Jour. Food Hyg. Soc. Japan. 15: 252.

Mizutani, T., et al. 1977. A comparative study on accumulation and elimination of tetrachlorobiphenyl isomers in mice. Bull. Environ. Toxicol. Contam. 18: 452.

Nagasaki, H., et al. 1972. Hepatocarcinogenicity of polychlorinated biphenyls in mice. Gann. 63: 805.

Nagayama, J., et al. 1975. Chlorinated dibenzofurans in Kanechlors and rice oils used by patients with Yusho. Fukuoka Acta. Med. 66: 593.

National Cancer Institute. 1978. Bioassay of Aroclor 1254 for possible carcinogenicity. Carcin. Tech. Rep. Ser. No. 38. DHEW Publ. No. (NIH) 78-838.

National Institute for Occupational Safety and Health. 1977. Criteria for a recommended standard. Occupational exposure to polychlorinated biphenyls (PCBs). DHEW (NIOSH) Publ. No. 77-225.

Nimmo, D.R., et al. 1975. Toxicity of Aroclor® 1254 and its physiological activity in several estuarine organisms. Arch. Environ. Contam. Toxicol. 3: 22.

Nisbet, I.C. and A.F. Sarofim. 1972. Rates and routes of transport of PCBs in the environment. Environ. Health Perspect. 1: 21.

Nishizumi, M. 1970. Light and electron microscope study of chlorobiphenyl poisoning in mouse and monkey liver. Arch. Environ. Health. 21: 620.

Nishizumi, M. 1976. Enhancement of diethylnitrosamine hepatocarcinogenesis in rats by exposure to polychlorinated biphenyls or phenobarbital. Cancer Lett. 2: 11.

Norstrom, R.J., et al. 1976. A bioenergetics-based model for pollutant accumulation by fish. Simulation of PCB and methyl-mercury residue levels in Ottawa river yellow perch, Perca flawescens. Jour. Fish Res. Board Can. 33: 248.

Odashima, S. 1976. The Cooperative Development in Japan of Methods for Screening Chemicals for Carcinogenicity. In: R. Montesano, et al. (eds.), Screening Tests in Chemical Carcinogenesis. Publ. No. 12. Inter. Agency Res. Cancer, Lyon, France. p. 61.

Okumura, M., et al. 1974. Correlation between blood PCB and serum triglyceride levels in patients with PCB poisoning. Fukuoka Acta. Med. 65: 84. (Jap.)

Orberg, J. and J.E. Kihlstrom. 1973. Effects of long-term feeding of polychlorinated biphenyls (PCB, Clophen A60) on the length of the oestrous cycle and on the frequency of implanted ova in the mouse. Environ. Res. 6: 176.

Ouw, H.K., et al. 1976. Use and health effects of Aroclor 1242, a polychlorinated biphenyl in an electrical industry. Arch. Environ. Health. 31: 189.

Paribok, V.P. 1954. Effects of chlorinated diphenyl (solvol) on the skin and its resorption. Formakol Toksikol. 17: 51. (Rus.) In: National Institute of Occupational Safety and Health. 1977. Criteria for a recommended standard... Occupational exposure to polychlorinated biphenyls (PCBs). DHEW (NIOSH) Publ. No. 77-225.

Peakall, D.B. 1975. PCBs and their environmental effects. CRC Crit. Rev. Environ. Cont. 5: 469.

Platonow, N.S. and L.H. Karstad. 1973. Dietary effects of polychlorinated biphenyls on mink. Can. Jour. Comp. Med. 37: 90.

Puccinelli, V. 1954. On chloracne. Med. d Lavoro. 45: 131. (Italy)

Reuber, M.D. 1968. Histogenesis of cholangiofibrosis and well differentiated cholangiocarcinoma in Syrian hamsters given 2-acetoamidofluorene or 2-diacetoamidofluorene. Gann. 59: 239.

Ringer, R.K., et al. 1972. Effect of dietary polychlorinated biphenyls on growth and reproduction of mink. 164th Natl. Meet. Am. Chem. Soc. 12: 149.

Risebrough, R.W. and B. deLappe. 1972. Accumulation of polychlorinated biphenyls in ecosystems. Environ. Health Perspect. 1: 39.

Safe, S., et al. 1975. The mechanism of chlorobiphenyl metabolism. Jour. Agric. Food Chem. 23: 851.

Safe, S., et al. 1976. Metabolism of 4,4'-dihalogenobiphenyls. Jour. Chem. Soc. Perkin Trans. 1: 357.

Schaible, P.J. 1970. Nutrition and Feeding. Section III. In: The Blue Book of Fur Farming. Editorial Service Co., Milwaukee, Wisconsin.

Schmoldt, A., et al. 1974. Induction of rat liver enzymes by polychlorinated biphenyls (PCBs) in dependence on the dose and chlorine content. Arch. Toxicol. 32: 69.

Schwartz, L. 1936. Dermatitis from synthetic resins and waxes. Am. Jour. Pub. Health. 26: 586.

Sivalingan, P.M., et al. 1973. Modes of inhibitory effects of PCBs on oxidative phosphorylation of mitochondria. Bull. Environ. Contam. Toxicol. 10: 242.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

Stewart, H.C. and K.C. Snell. 1957. The histopathology of experimental tumors of the liver of the rat. A critical review of the histopathogenesis. Acta. Un. Int. Control. Cancer. 13: 770.

Street, J.C. and R.P. Sharma. 1975. Alteration of induced cellular and humoral immune responses by pesticides and chemicals of environmental concern: Quantitative studies of immunosuppression by DDT, Aroclor 1254, carbaryl, carbofuran, and methyl parathion. Toxicol. Appl. Pharmacol. 32: 587.

Street, J.C., et al. 1969. Comparative effects of polychlorinated biphenyls and organochlorine pesticides in induction of hepatic microsomal enzymes. Pap. presented at 158th Natl. Meet. Am. Chem. Soc., New York.

Sundstrom, G., et al. 1976a. The metabolism of chlorobiphenyls -A review. Chemosphere. 5: 267.

Sundstrom, G., et al. 1976b. The metabolism of 2,2',4,4',5,5'-hexachlorobiphenyl by rabbits, rats and mice. Chemosphere. 4: 249.

Thomas, P.T. and R.D. Hinsdill. 1978. Effect of polychlorinated biphenyls on the immune responses of Rhesus monkeys and mice. Toxicol. Appl. Pharmacol. 44: 41.

Tombergs, H.P. 1972. The PCB situation in Germany. Environ. Health Perspect. 1: 179.

Tucker, R.K. and D.G. Crabtree. 1970. Handbook of toxicity of pesticides to wildlife. Bur. Sport Fish. Wildl. Resour. Publ. 84. U.S. Dept. Inter., Washington, D.C.

Tuey, D.B. and H.B. Matthews. 1977. Pharmacokinetics of 3,3',5,5'-tetrachlorobiphenyl in the male rat. Drug Metab. Dispo. 5: 444.

Turner, J.C. and R.S. Green. 1974. Effect of polychlorinated biphenyl (Aroclor 1254) on liver microsomal enzymes in the male rat. Bull. Environ. Contam. Toxicol. 12: 669.

Uchiyama, M., et al. 1974. Co-carcinogenic effect of DDT and PCB feedings on methylcholanthrene-induced chemical carcinogenesis. Bull. Environ. Contam. Toxicol. 12: 687.

Urabe, H. 1974. Forward to the fourth report of the study on Yusho and PCB. Fukuoka Acta. Med. 65: 1. (Jap.)

U.S. EPA. 1976a. Criteria Document PCBs. Office of Water Planning and Standards, U.S. Environ. Prot. Agency, Washington, D.C. EPA 440/9-76-021.

U.S. EPA. 1976b. Quality Criteria for Water. U.S. Environ. Prot. Agency, Washington, D.C. U.S. Government Printing Office, Pub. 0-222-904. p. 193.

U.S. EPA. 1980. Seafood consumption data analysis. Stanford Research Institute International, Menlo Park, California. Final Report, Task 11. Contract No. 68-01-3887.

Vainio, H. 1974. Enhancement of microsomal drug oxidation and glucuronidation in rat liver by an environmental chemical polychlorinated biphenyl. Chem. Biol. Interact. 9: 379.

Van Miller, J.P., et al. 1975. Distribution and metabolism of ^3H-2,5,2',5'-tetrachlorobiphenyl in rats. Proc. Soc. Exp. Biol. Med. 148: 682.

Veith, G. 1975. Baseline concentrations of polychlorinated biphenyls and DDT in Lake Michigan fish, 1971. Pestic. Monitor Jour. 9: 21.

Veith, G.D., et al. 1977. Residues of PCBs and DDT in the Western Lake Superior ecosystem. Arch. Environ. Contam. Toxicol. 5: 487.

Villeneuve, D.C., et al. 1971a. Effects of PCB administration on microsomal enzyme activity in pregnant rabbits. Bull. Environ. Contam. Toxicol. 6: 120.

Villeneuve, D.C., et al. 1971b. The fetotoxicity of polychlorinated biphenyl mixture (Aroclor 1254) in the rabbit and in the rat. Environ. Physiol. 1: 67.

Villeneuve, D.C., et al. 1972. Modification of pentobarbitol sleeping times in rats following chronic PCB ingestion. Bull. Environ. Contam. Toxicol. 7: 264.

Vos, J.G. and R.B. Beems. 1971. Dermal toxicity studies of technical polychlorinated biphenyls and fractions thereof in rabbits. Toxicol. Appl. Pharmacol. 19: 617.

Vos, J.G. and T. DeRoij. 1972. Immunosuppressive activity of a polychlorinated biphenyl preparation on the humoral immune response in guinea pigs. Toxicol. Appl. Pharmacol. 21: 549.

Vos, J.G. and J.H. Koeman. 1970. Comparative toxicologic study with polychlorinated biphenyls in chickens with special reference to porphyria edema formation, liver necrosis, and tissue residues. Toxicol. Appl. Pharmacol. 17: 656.

Vos, J.G. and E. Notenboom-Ram. 1972. Comparative toxicity study of 2,4,5,2',4',5'-hexachlorobiphenyl and a polychlorobiphenyl mixture in rabbits. Toxicol. Appl. Pharmacol. 23: 563.

Vos, J.G. and H. van Genderen. 1973. Toxicological Aspects of Immunosuppression. In: W.B. Deichman, (ed.), Pesticides in the Environment. A Continuing Controversy. 8th Int. Conf. Toxicol. Occup. Med., Miami. Intercontinental Medical Book Co., New York.

Vos, J.G., et al. 1970. Identification and toxicological evaluation of chlorinated dibenzofuran and chlorinated naphthalene in two commercial polychlorinated biphenyls. Food Cosmet. Toxicol. 8: 625.

Willett, L.B. and J.F. Hess, Jr. 1975. Polychlorinated biphenyl residues in silos in the United States. Residue Rev. 55: 135.

Wyndham, C., et al. 1976. The *in vitro* metabolism, macromolecular binding and bacterial mutagenicity of 4-chlorobiphenyl, a model PCB substrate. Res. Commun. Chem. Pathol. Pharmacol. 15: 563.

Yakushiji, T., et al. 1977. PCB and organochlorine pesticides in mothers' milk, blood and foods. Paediatrician. 6: 28.

Yamashita, F. 1977. Clinical features of polychlorbiphenyls (PCB)-induced fetopathy. Paediatrician. 6: 20.

Yobs, A.R. 1972. Levels of polychlorinated biphenyls in adipose tissue of the general population of the nation. Environ. Health Perspect. 1: 79.

Yoshimura, T. 1974. Epidemiological study on Yusho babies born to mothers who had consumed oil contaminated by PCB. Fukuoka Acta. Medica. 65: 74.

Young, D.R., et al. 1976. Marine Inputs of Polychlorinated Biphenyls off Southern California. In: Natl. Conf. Polychlor. Biphenyls. Nov. 19-21, Chicago, Illinois. EPA 560/6-75-004. Off. Toxic Subst., U.S. Environ. Prot. Agency, Washington, D.C.

APPENDIX

Summary and Conclusions Regarding the Carcinogenicity of Polychlorinated Biphenyls*

Polychlorinated biphenyls (PCBs) are prepared by the chlorination of biphenyl and are complex mixtures containing isomers of chlorobiphenyls with different chlorine content.

Because of the widespread industrial use of PCBs, their long half-life, and the documented disease-producing capability of these compounds in several species, regulations have been promulgated banning most of the manufacturing, processing, and distribution of PCBs in the United States (44 FR 106).

Human studies concerning the possible carcinogenicity of PCBs have involved small numbers of individuals and provide little information about exposure. Although these studies are only marginally useful in describing the carcinogenicity of PCBs, the incidence of malignant neoplasms in "Yusho" patients and in industrial workers exposed to Aroclor 1254 suggests that human exposure to PCBs is associated with an increased risk of neoplasia.

In two separate studies, PCBs have been reported to induce hepatocellular carcinomas in both mice and rats (male mice fed Kanechlor 500 at 500 ppm and female Sherman rats fed Aroclor 1260 at 100 ppm).

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*This summary has been prepared and approved by the Carcinogens Assessment Group of EPA on June 15, 1979.

In an NCI bioassay, Aroclor 1254 was not carcinogenic in Fischer 344 rats, but the high frequency of hepatocellular proliferative lesions was considered to be the result of treatment and carcinomas of the gastrointestinal tract possibly associated with treatment. In one other mouse study and three other rat studies, various PCBs induced proliferative lesions of the liver which might be indicative of carcinogenicity. The most commonly seen lesions were adenofibrosis (cholangiofibrosis) and neoplastic nodules.

A correlation between degree of chlorination and tumor inducing potential was observed in both mouse and rat species. The most highly chlorinated preparations were also the most potent tumor inducers with the exception of Aroclor 1254 which was more potent than Aroclor 1260 in one rat study. Where examined, female rats were found to be more sensitive than males. No comparisons of sex related effects were made in mice.

PCBs have been reported to be co-carcinogens, initiators, and promotors in both mouse and rat species.

The mutagenicity of different PCB preparations has been evaluated in several test systems with conflicting results. In one study, the single isomer 4-chlorobiphenyl was reported to be highly mutagenic in *Salmonella typhimurium* strain TA1538 after liver microsomal activation, while Aroclor 1221 was reported to be less mutagenic and Aroclors 1254, 1268, and 2,5,2',5'-tetrachlorobiphenyl were inactive. The fact that mutagenic activity decreased with increasing chlorination is consistent with the characteristic insensitivity of the Ames test to chlorinated hydrocarbons. In other test systems, Kanechlor 300 inhibited bacterial DNA repair deficient cells and induced cytogenetic abnormalities in Yoshida sarcoma cells. Kanechlor 500 tested positive in a mouse bone marrow cytogenetic analysis.

In summary, carcinogenic responses have been induced in mice and rats. These results, together with positive mutagenic responses and suggestive epidemiologic evidence, constitute substantial evidence that PCBs are likely to be human carcinogens.

The water quality criterion for PCBs is based on the Kimbrough, et al. (1975) study on the induction of hepatocellular carcinomas and neoplastic nodules in female Sherman strain rats fed 100 ppm Aroclor 1260. It is concluded that the water concentration of PCBs should be less than 0.79 ng/l ($\sim$0.8 ng/l) in order to keep the lifetime cancer risk below 10^{-5}.

Summary of Pertinent Data

The water quality criterion for PCBs is derived from the hepatocellular carcinoma and neoplastic nodule response of Sherman strain female rats fed Aroclor 1260 at a nominal dietary level of 100 ppm (Kimbrough, et al. 1975). A time-weighted average dose of 88.4 ppm (i.e., the dose varied between 70 and 107 ppm in the Kimbrough, et al. study) was administered for approximately 21.5 months and the animals were observed for an additional six weeks before terminal sacrifice. The criterion is calculated from the following parameters where the adjustment factor of 0.05 represents the fraction of food consumed in relation to body weight:

Dose (mg/kg/day)	Incidence (No. responding/No. tested)
0	1/173
4.42 (i.e., 88.4 ppm x 0.05)	170/184

le = 645 days
Le = 730 days
L = 730 days

w = 0.400 kg
R = 31,200 l/kg

With these parameters the carcinogenic potency factor for humans is 4.3396 $(mg/kg/day)^{-1}$. The resulting water concentration of PCBs calculated to keep the individual lifetime cancer risk below 10^{-5} is 0.79 ng/l.